Pathogenesis & pathology of

parkinsonism

Including: **Lecture Slides + Our Notes**

The colors indicate: **Important Points** + **Team notes**

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Degenerative brain disease

- The term “Degenerative”:

  reflecting an underlying cellular degeneration of neurons in the brain
- Symptoms depend on part of brain involved (degenerated).

Parkinson’s Disease & Parkinsonsim:

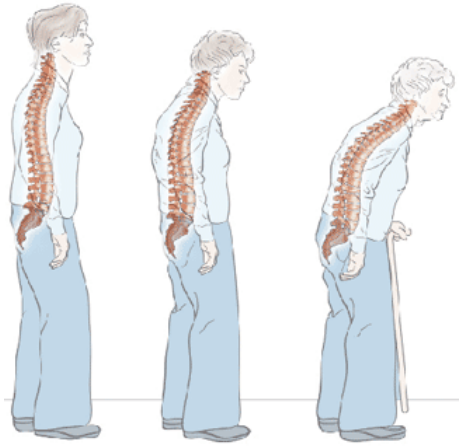
If there’s a disease or syndrome, causing symptoms of Parkinson’s (e.g. resting tremors, festinating gait ..etc) and we **know** the cause → we call it **Parkinsonism**

If there’s a disease, causing symptoms of Parkinson’s (e.g. resting tremors, festinating gait, ..etc) and we **DO NOT know** the cause → we call it **(Idiopathic) Parkinson’s Disease**

Parkinson's

- A clinical syndrome **characterized by:**
  - ✓ diminished facial expression (masked facies)
  - ✓ stooped posture *
  - ✓ slowness of voluntary movement
  - ✓ festinating gait * (shortened, accelerated steps)
  - ✓ rigidity
  - ✓ "pill-rolling" tremor (Tremors at rest)

Stooped: flexed posture (see picture)



- Motor disturbances that are seen in a number of conditions that share **damage to dopaminergic neurons** of the **substantia nigra** or **their projection** to the striatum

Parkinson's (in general) will affect the basal ganglia.

[specifically the substantia nigra in the pars compacta area **- which produces dopamine]**

Dopamine: is an inhibitory neurotransmitter. So when it doesn't work, there is no inhibition → rigidity

when substantia nigra is not working → the extra pyramidal system takes the upper hand instead of substantia nigra → It would be so high and cause tremors at rest + rigidity

→ **so we produce a lesion to the extra pyramidal system to stop its affect –** [optional procedure]

* Parkinsonism *

- Induced by:
  - drugs that affect these neurons, particularly dopamine antagonists and toxins (neuroleptics)
  - Post-encephalitic parkinsonism (associated with the influenza pandemic)
  - *Idiopathic Parkinson disease* **Idiopathic**: without a known cause
    (the most common neurodegenerative disease associated with parkinsonism)
  - **Other:** Neuro-degenreative diseases
  - **Rare:** *head trauma, stroke*

* (Idiopathic) Parkinson's Disease *

- **Diagnosis:**
  - progressive parkinsonism
    (the symptoms of parkinson's are progressive)
  - absence of a toxic or other known underlying etiology
  - clinical response to L-dihydroxyphenylalanine (L-DOPA) treatment

Diagnosing

•When we want to diagnose **Parkinson's disease,** we first exclude all other diseases possible (diagnosis with exclusion)

•**Diagnostic + Therapeutic**
(giving the patient **L-DOPA** sublingually – under the tongue – and if he responds to this treatment, then we are sure it is parkinson's disease)

•We **must** know all about **family history**.

- **Predisposing Factors**
  - ✓ 6-8 decades
  - ✓ more than 2% in North America develop disease
  - ✓ men more than women
  - ✓ 22/100,000 = crude prevalence rate in Saudi population

❖ Most Parkinson disease is **sporadic**
(occurring at irregular places -scattered or isolated)
+ also **autosomal dominant** and **recessive** forms of the disease

- **Genetic analysis:**
  specific causal mutations
  For example **α-synuclein mutations** cause autosomal dominant Parkinson disease
  (as can gene duplications & triplications: giving extra copies of gene when growing up**)**

❖ **Even if it is not caused by gene mutations**
the **diagnostic feature** of the disease: **the Lewy body**
→ is an inclusion containing **α-synuclein**

α-synuclein : A widely expressed neuronal protein that is involved in synaptic transmission and other cellular processes.

- How the alterations in sequence or protein levels result in disease is unclear
- The presence of **α-synuclein** in the **Lewy bodies** has suggested that defective degradation of the protein in the proteasome might play a role.
  This is supported by the identification of two other genetic loci:
  - Genes encoding parkin: **E3 ubiquitin ligase**
  - **UCHL-1**
    (an enzyme involved in recovery of ubiquitin from proteins targeted to the proteasome)

Ubiquitin :are a small regulatory proteins, that directs proteins to recycling.
-It binds to proteins and labels them for destruction.
-Its tag directs proteins to the proteasome.

Proteasome: an organelle in the cell that degrades and recycles unneeded proteins , (it breaks down proteins that have been tagged (attached by ubiquitin).

Parkin: Ligase (an enzyme)

The genetic findings in parkinson's disease:

Genetic analysis has identified specific casual mutations, such as :

1- α-synuclein

this mutation causes autosomal dominant PD.

2- Gene duplication and triplication can cause autosoamal dominant PD.

3- genes encoding parkin

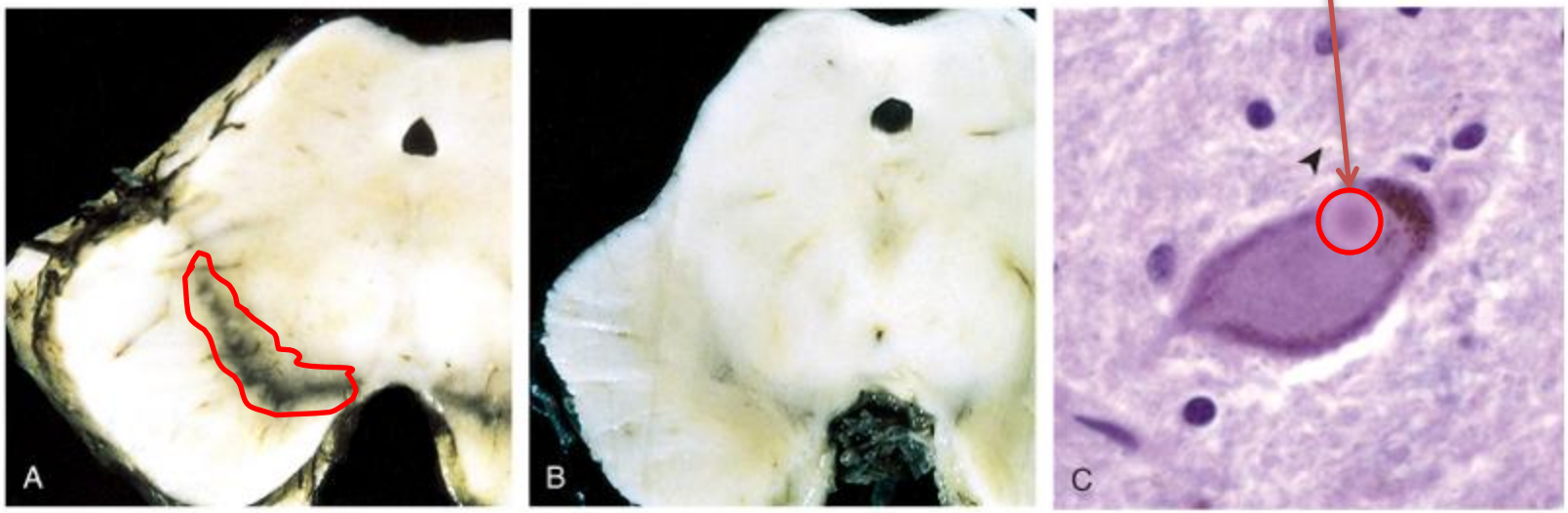
4- UCHL-1

α-synuclein → accumulates → form the **lewy bodies**
(it was not degraded in the proteasomes - wasn't recycled)

Lewy body

Normal
Substantia Nigra

Parkinson's Disease
Substanita Nigra



- **Lewy bodies** are bodies characterized by densely pinkish-color in the center and light color at the periphery.
  They are not specific in parkinson's disease, you may find them in other diseases, **but their finding confirms the diagnosis of the it.**

Even in cases of Parkinson disease that are not caused by mutations of any gene, the diagnostic feature of the disease is –the Lewy Body- (is an inclusion containing α-synuclein), (we can only see the lewy bodies by autopsy – after death only)

- **Macroscopic:** (areas affected - gross)

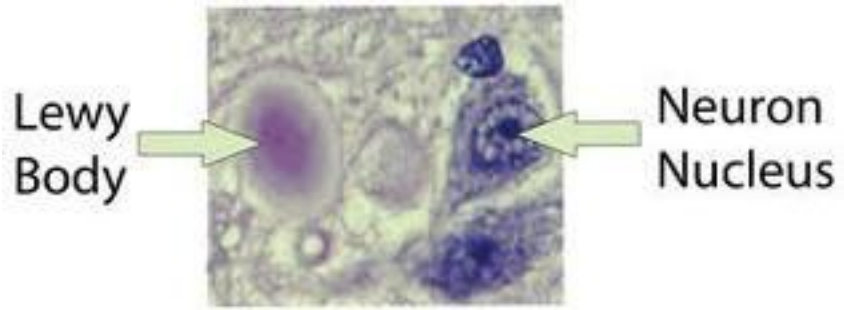
  pallor of the **substantia nigra** and **locus ceruleus**

  Locus ceruleus: is a nucleus in the brain stem, in the dorsal wall of the rostral Pons, in the lateral floor of the fourth ventricle.

- **Microscopic:**
  - loss of the pigmented, neurons in these regions (previous slide fig B)
  - associated with gliosis
  - **Lewy bodies** may be found in some of the remaining neurons (previous slide, fig C)

Lewy Bodies

- Single or multiple, intracytoplasmic, eosinophilic, round to elongated inclusions that often have a dense core surrounded by a pale halo
- Ultrastructurally, Lewy bodies are composed of fine filaments, densely packed in the core but loose at the rim
- These filaments are composed of ***α-synuclein***, along with other proteins



- **Clinical Features**
  - Usually progresses over 10 to 15 years
  - eventual severe motor slowing to the point of near immobility
  - death is usually the result of intercurrent infection or trauma from frequent falls caused by postural instability

the most frequent infection in elderly people.

Its complications:

-pneumonia (predisposed to infections especially in lungs)

-bedsores due to immobility (not moving for long time)

-rigidity becomes SO STRONG till they cant move

- About 10% to 15% of individuals with Parkinson disease develop dementia, with the incidence increasing with advancing age

- Characteristic features of this disorder include a fluctuating course and hallucinations

- Also they have pathologic evidence of **Alzheimer disease.**

- **Dimentia** happens due to accumulation of **lewy bodies**

- **Treatment**
  - L-DOPA therapy is often extremely effective in symptomatic treatment, but it does not significantly alter the progressive nature of the disease
  - Over time, L-DOPA becomes less effective at providing the patient with symptomatic relief and begins to cause fluctuations in motor function on its own
  - L-Dopa → not a permanent treatment because we don't want the patient to get used to it.

- **Therapeutic approaches:** are many, including: transplantation, gene therapy, and stem cell injection.

- **Neurosurgical Approaches:**
  the placement of lesions in the extrapyramidal system to stop it from being the upper hand