

# **III. Parkinson Disease**

- *Parkinsonism* is a clinical syndrome characterized by motor disturbances and may be seen in a range of diseases that damage dopaminergic neurons, which project from the substantia nigra to the striatum.

## **Parkinsonism characterized by:**

- a. Diminished facial expression (often termed *masked facies*),
- b. Stooped posture,
- c. Slowing of voluntary movement,
- d. Festinating gait (progressively shortened, accelerated steps),
- e. Rigidity, and a “pill-rolling” tremor.

- Causes:

1. Several neurodegenerative diseases , main example is Parkinson disease (PD)
2. Toxins that selectively damage the dopaminergic system

- a. MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine), causes an acute parkinsonian syndrome and destruction of neurons in the substantia nigra

b. Pesticide exposure

3. Post encephalitic parkinsonism that followed pandemic influenza in 1918

- Thee diagnosis **of PD** can be based on:
  1. The presence of triad of parkinsonism—tremor, rigidity, and bradykinesia
  2. In the absence of a toxic or other known underlying etiology.
  3. . And is confirmed by symptomatic response to L-DOPA replacement therapy

## Note

- Although the diagnosis of PD is based in large part on the presence of the motor symptoms, there is clear evidence that the disease is not restricted to dopaminergic neurons or to the basal ganglia



- There is evidence that PD is a progressive diseases with stages:
  1. It begins lower in the brainstem
  2. Involves substantia nigra
  3. Then involves cerebral cortex leading to cognitive impairment

# Pathogenesis.

- PD is associated with :
  1. Protein accumulation and aggregation
  2. Mitochondrial abnormalities,
  3. and neuronal loss in the substantia nigra and elsewhere in the brain.

# Pathogenesis in sporadic cases

## Postulated theories

1. Oxidative injury may play a role
  - Neuromelanin , a product of dopamine auto-oxidation is capable of forming a complex with iron and potentiates generation of free radicals and oxidative injury

2. Missence mutations in the gene encoding  $\alpha$ -synuclein causing extra copies of  $\alpha$ -synuclein (which is presynaptic neurotransmitter) favors intracellular aggregation and protofibril formation of this protein

and dopamine reacts with it

- And this slows the process of protofibrils to fibril conversion and the protofibrils are toxic to the neurons and this may explain dopaminergic selectivity of  $\alpha$ -synuclein associated PD

3. Age related reduced proteasome degradation of  $\alpha$ -synuclein may result in an increased intracellular accumulation of synuclein protofibrils

## Note

- While most PD is sporadic, a series of genetic causes have been identified that shed light on its pathogenesis.

## 1. Autosomal dominant parkinson disease

- a. Caused by point mutations and amplifications of the region of chromosome 4q21 that contains the gene which encodes *α-synuclein*, an abundant lipid-binding protein normally associated with synapses.



- This protein was then demonstrated to be a major component of the Lewy body, which is the diagnostic hallmark of PD

- $\alpha$ -synuclein form small which appear to be toxic to neurons.

- b. Mutations in the gene encoding *LRRK2*  
(leucine-rich repeat kinase 2)
  - Are a more common cause of autosomal dominant PD and are found in some sporadic cases of the disease.

- LRRK2 is a cytoplasmic kinase.
- The mutations increase the kinase activity of LRRK2, which leads to hyperphosphorylation of normal targets

## 2. Autosomal recessive PD

- *Caused by Mutations in the genes* that encode the proteins DJ-1, PINK1, and parkin.
- a. DJ-1 acts as a transcriptional regulator, but in settings of oxidative stress it can relocate to the mitochondria and have cytoprotective effects.

- So loss of function mutation in DJ1 leads to oxidative stress in the mitochondria and damage to neurons by free radicals

## b. PINK1

- Is a kinase that is degraded in the mitochondria under normal circumstances;
- And with mitochondrial dysfunction, it recruits parkin, which is an E3 ubiquitin ligase.

- Under normal circumstances, the combination of PINK1 and parkin results in clearance of dysfunctional mitochondria through mitophagy



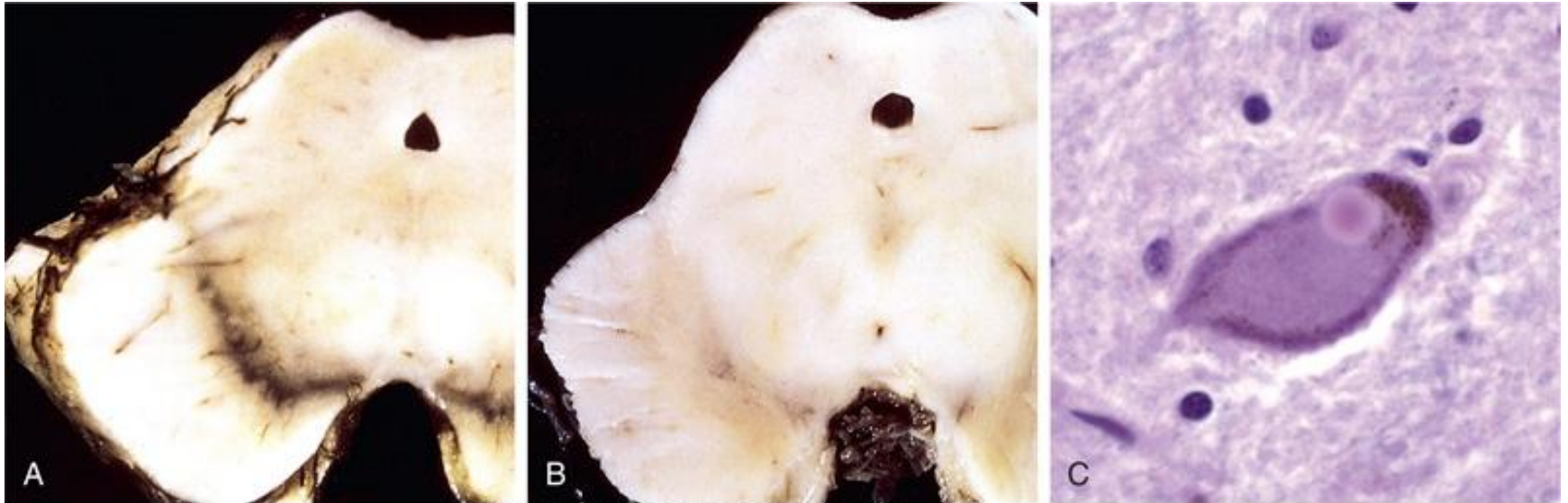
- Therefore loss of function mutations in these genes lead to loss of mitophagy of dysfunctional mitochondria
- So dysfunctional mitochondria will lead to formation of large amounts of free radicals that will damage neurons

# Morphology

## **Macroscopic appearance:**

- A characteristic finding in PD is pallor of the substantia nigra and locus ceruleus, which is due to loss of the pigmented, catecholaminergic neurons in these regions.

# Parkinson disease



Kumar et al: Robbins Basic Pathology, 9e.  
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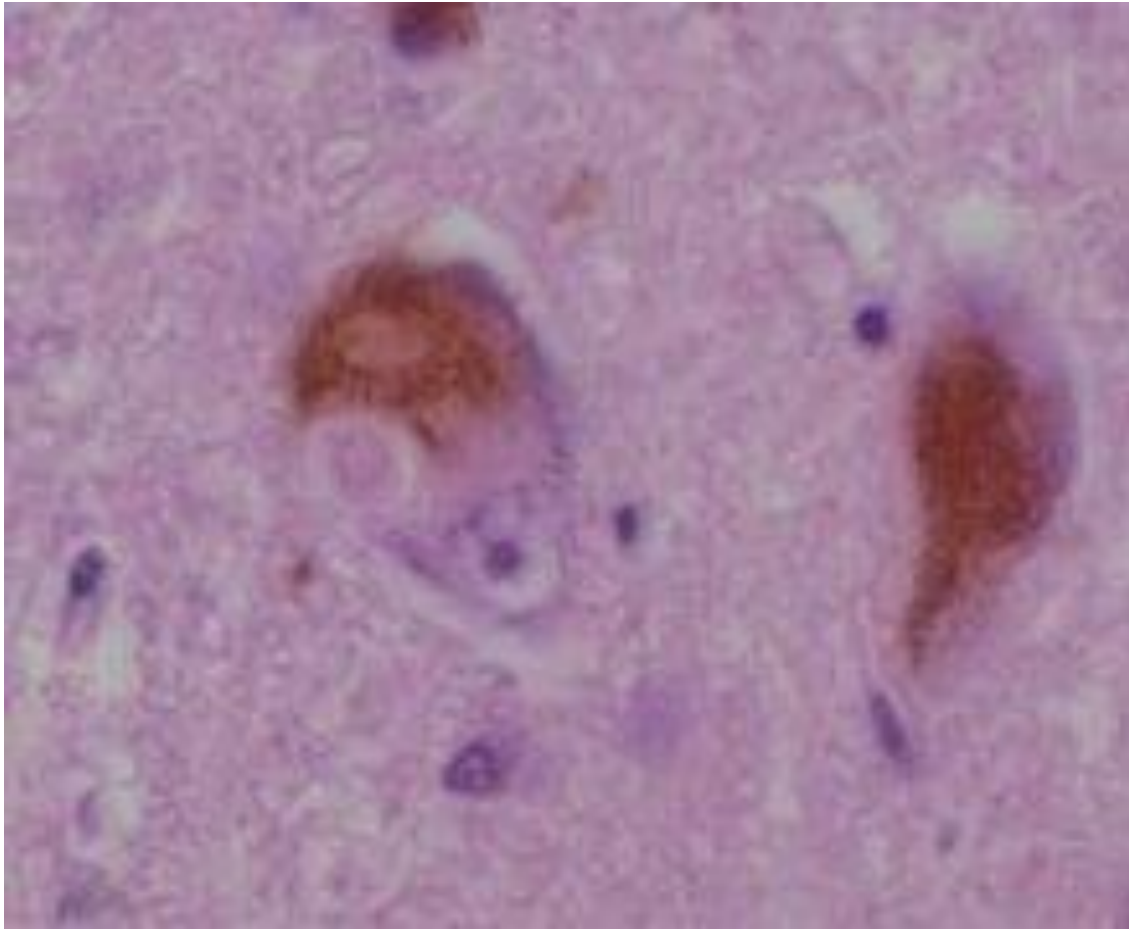
# Microscopic findings

1. Loss of the pigmented, catecholaminergic neurons in these regions
2. associated with gliosis.

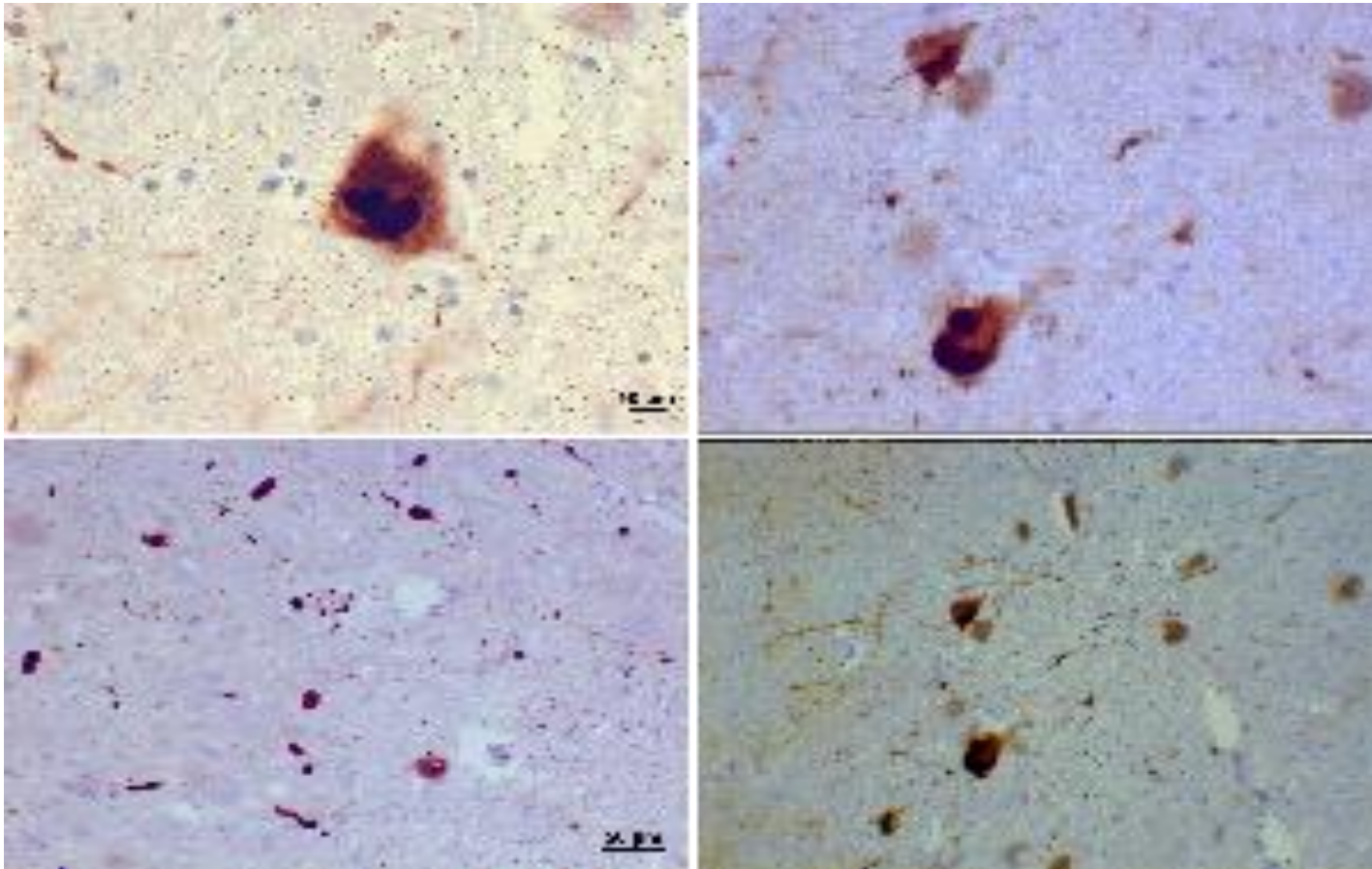
## 2. Lewy bodies

- May be found in those neurons that remain viable
- and these are single or multiple,
- intracytoplasmic, eosinophilic, inclusions that often have a dense core surrounded by a pale halo

# Lewy bodies



# Immunostains for $\alpha$ -synuclein



- **Neurochemistry of parkinson disease**
  - Loss of cells from substantia nigra pars compacta(SNc) leads to reduced inhibitory dopaminergic input into the striatum
  - This in turn results in increase release of GABA from striatum to lateral globus pallidus



3. Decrease GABA release from lateral globus to Subthalamic nucleus ,
4. therefore the subthalamic nucleus production of excitatory glutamate increases to the medial globus pallidus
5. and then medial globus pallidus will increase its release of inhibitory GABA to the thalamus

- GABA is inhibitory so it will lead to decrease glutamate from thalamic nuclei to the cortex and this leads to akinetic rigid syndrome of parkinson