

Parkinsonism:

Parkinson's is increasingly seen as a complex neurodegenerative disease with a sequence of progression.

Neurodegenerative disease:

These are a group of disorders characterized by neuronal loss and generally an accumulation of insoluble intracellular or extracellular material in certain brain regions.

Parkinson's disease is primarily associated with the gradual loss of cells in the substantia nigra of the brain.

This area is responsible for the production of dopamine.

Dopamine:

It is a chemical messenger that transmits signals between two regions of the brain to coordinate activity.

Ex - It connects substantia nigra and the corpus striatum to regulate muscle activity.

① It generally affects the elderly and is estimated to afflict more than 1% of individuals over the age of 65.

Sub:

Etiology / cause:

- ① Most causes are of idiopathic parkinsonism.
- ① Viral inflammation.
- ① Brain trauma, stroke.
- ① poisoning by manganese, carbon monoxide, pesticide, or 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine.
- ① Intoxication with MPTP, a byproduct of the synthesis of an illegal meperidine analogue, produces a condition closely resembling parkinsonism.
- ① Genetic predisposition, environmental toxins ageing.
- ① Drug induced (iatrogenic parkinsonism) which is often is a complication of antipsychotic therapy, especially following the use of the the butyrophenone and phenothiazine drug classes.

[Unlike idiopathic parkinsonism, striatal content of dopamine is not reduced by administration of these drugs. In contrast they produced a functional decrease in dopamine activity by blocking the action of dopamine on postsynaptic dopamine receptors]

Clinical Findings (Symptoms):

- ① There is a progressive loss of dopamine ~~not~~ neurons with age. Relatively smooth functioning of motor control is maintained until neuronal loss is such that in it cause can 80% reduction of dopamine in the striatum.

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① The most prominent features of parkinsonism are tremor, rigidity and bradykinesia.

① Tremors - are often unilateral in onset, present at rest and cease during voluntary movement.

Rigidity, is increased muscle tone.

① Bradykinesia:

It is an extreme slowness of movement. It results in a typical stooped posture when the person is standing or walking and absence of normal arm swinging movements.

① The absence of facial expression results from loss of facial ~~muscle~~ muscle function.

① Inability to swallow leads to drooling, while bradykinesia of the muscles in the larynx results in change in voice quality.

① Orthostatic hypotension may also be observed and may complicate therapy.

① Cognitive dysfunction and dementia are also seen in a small percentage of parkinson's disease patients, especially the elderly.

Sub:

Genetic factors that raise the risk of parkinson's

- ① Certain genes have been found that may be associated with parkinson's disease.
- ① At least 15-20% of parkinson's disease patients have a close relative who has parkinsonian symptoms.
- ① There may be more than one genetic factor in causation of parkinson's disease.
- ① In addition genetic factors may be combined with environmental factors as well.

Free radicals:

These are unstable molecules produced during normal chemical reactions in the body. When they interact with other molecules they have the ability to damage tissues like neurons.

Aging:

With age there is a normal decline of the dopamine producing neurons, which leads to the premature loss of dopamine.

Pathophysiology:

The most prominent pathological findings in parkinson's disease are degeneration of the darkly pigmented dopamine neurons in the substantia nigra, loss of dopamine in the neostriatum, and the presence of intracellular inclusion bodies known as Lewy bodies.

Other neuronal populations are also affected in parkinson's disease to a much lesser extent but they may contribute to some of the other pathology seen in Parkinsonism.

Ex - cognitive decline, depression, and dementia

Therapy of parkinsonism:

- 1.) Levodopa, as the immediate precursor of dopamine, increases dopamine production within the basal ganglia.
- 2.) MAO-B inhibitors block a major pathway in dopamine metabolism and thus increase the duration of action of dopamine.
- 3.) Dopamine receptor agonists directly activate dopamine receptors on postsynaptic neurons.
- 4.) Anticholinergic drugs block the increased excitatory activity of cholinergic interneurons on outflow pathway from the basal ganglia, which is secondary to a loss of inhibition actions of dopamine on these cholinergic interneurons.
- 5.) COMT inhibitors block an alternate pathway in the metabolism of dopamine.

Synthesis of Dopamine:

