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LITERATURE REVIEW: PARKINSON'S DISEASE

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Annotation

Parkinson's disease is a progressive neurodegenerative disorder characterized by the loss of dopaminergic neurons in the substantia nigra and the accumulation of α-synuclein aggregates known as Lewy bodies. Clinically, the disease presents with cardinal motor symptoms such as resting tremor, bradykinesia, and rigidity, while a wide range of non-motor manifestations—including cognitive impairment, autonomic dysfunction, sleep disturbances, and mood disorders—often precede motor onset. Modern therapeutic strategies are primarily symptomatic and aim to restore dopaminergic transmission through pharmacological treatments or deep brain stimulation. Despite significant advances, no current therapy effectively halts or reverses neurodegeneration. Ongoing research focuses on biomarkers, genetic mechanisms, immunotherapies targeting α-synuclein, and neuroprotective approaches to modify disease progression.

Keywords

Parkinson's disease; neurodegeneration; α-synuclein; Lewy bodies; dopaminergic neurons; basal ganglia; motor symptoms; non-motor symptoms; deep brain stimulation; neuroprotection.

Introduction. Parkinson's disease (PD) is one of the most prevalent neurodegenerative disorders, second only to Alzheimer's disease. It affects approximately 1–2% of individuals over the age of 65 and represents a major cause of disability among older adults. PD has traditionally been defined as a movement disorder due to its characteristic motor manifestations—resting tremor, bradykinesia, rigidity, and postural instability. However, accumulating evidence indicates that the disease is far more complex, involving widespread neurobiological changes and a broad spectrum of non-motor symptoms.

The underlying pathogenesis of PD is linked to the progressive degeneration of dopaminergic neurons in the substantia nigra pars compacta, which results in an imbalance of basal ganglia circuits responsible for motor control. A pathological hallmark of the disease is the presence of intraneuronal inclusions known as Lewy bodies, primarily composed of misfolded α-synuclein. Genetic research has identified mutations in several key genes, such as SNCA, LRRK2, PINK1, and PARK2, which contribute to monogenic and early-onset forms of PD. Environmental risk factors—including exposure to pesticides and certain industrial chemicals—also play a significant role.

In recent decades, the clinical concept of PD has expanded to include non-motor symptoms that may precede motor onset by years. These include olfactory dysfunction, constipation, sleep disturbances, anxiety, depression, and cognitive decline. Such prodromal

features suggest that PD is not solely a dopaminergic disorder but a systemic neurodegenerative process involving multiple neurotransmitter systems and brain regions.

Despite considerable advances in pharmacological and surgical therapy, current treatments remain symptomatic. Levodopa remains the gold standard for alleviating motor symptoms, while dopamine agonists, monoamine oxidase-B inhibitors, and deep brain stimulation provide additional therapeutic benefit. Nevertheless, none of these interventions have been shown to alter the underlying disease course. This reality underscores the urgent need to develop disease-modifying therapies, reliable biomarkers for early diagnosis, and improved strategies for long-term patient care.

Epidemiology. PD is the second most prevalent neurodegenerative disorder after Alzheimer's disease. Its incidence increases with age, peaking between 60 and 70 years. Men are affected slightly more frequently than women. The rise in global prevalence is likely linked to expanding life expectancy, improved diagnostic criteria, and heightened awareness of early symptoms.

Etiology and Risk Factors. PD is considered a multifactorial disorder arising from interactions between genetic predisposition and environmental exposures.

Genetic Factors. Monogenic forms of PD have been associated with mutations in genes such as SNCA, LRRK2, PARK2 (parkin), PINK1, and DJ-1. These mutations are more common in early-onset or familial Parkinsonism and contribute to dysregulation of protein homeostasis and mitochondrial integrity. SNCA, encoding α-synuclein, is central to the aggregation processes typical of PD.

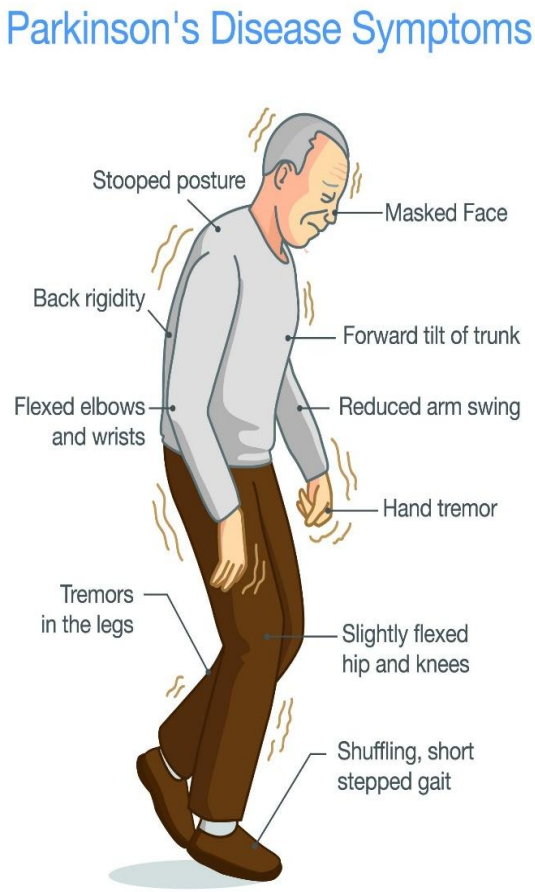
*Environmental Factors***.** Exposure to pesticides, heavy metals, and certain industrial solvents has been linked to increased PD risk. Conversely, epidemiological studies suggest an inverse relationship between PD risk and tobacco smoking or caffeine intake, although the biological mechanisms underlying these associations remain unclear.

Pathophysiology and Neuropathology. The hallmark neuropathological feature of Parkinson's disease (PD) is the progressive degeneration of dopaminergic neurons located in the substantia nigra pars compacta, a midbrain region responsible for supplying dopamine to the striatum. Loss of these neurons reduces dopamine availability within the nigrostriatal pathway, thereby impairing the ability of basal ganglia circuits to facilitate voluntary movement. The degeneration is gradual and often begins years before the onset of clinically recognizable motor symptoms. A defining pathological marker of PD is the formation of Lewy bodies and Lewy neurites, which represent intracellular aggregates primarily composed of misfolded α-synuclein together with ubiquitin and other proteins involved in cellular quality-control mechanisms. The presence of these inclusions reflects an abnormal protein metabolism and is considered a central feature of synucleinopathies.

On the neural circuit level, dopamine deficiency results in a disruption of the delicate balance between the direct (facilitatory) and indirect (inhibitory) pathways of the basal ganglia. Reduced stimulation of the direct pathway and excessive activation of the indirect pathway lead to increased inhibitory output from the internal segment of the globus pallidus to the thalamus. Consequently, thalamocortical drive decreases, limiting motor cortex activation and manifesting clinically as bradykinesia and rigidity. Additionally, altered firing patterns of the subthalamic

nucleus and increased abnormal oscillatory activity contribute to movement dysfunction and motor fluctuations.

Clinical Manifestations. The cardinal motor features of PD include:



- Resting tremor, often asymmetric;

- Muscle rigidity;

- Bradykinesia (slowness of movement).

In later disease stages, postural instability contributes to disability and falls.

Non-motor symptoms frequently precede motor signs by years and may include hyposmia, constipation, REM sleep behavior disorder, anxiety, depression, and mild cognitive impairment. The presence of prodromal symptoms indicates that PD involves widespread neurodegeneration beyond dopaminergic pathways.

Diagnosis. PD diagnosis remains clinical and is based on motor features and response to dopaminergic therapy. Dopamine transporter imaging (DaTSCAN) can support diagnostic accuracy by visualizing presynaptic dopaminergic deficits. MRI is typically used to exclude secondary parkinsonisms such as vascular lesions or normal-pressure hydrocephalus. Emerging biomarkers, particularly α-synuclein detection in cerebrospinal fluid or skin biopsies, are under investigation but not yet standardized for routine care.

Treatment Strategies. Current therapeutic approaches aim to restore dopaminergic signaling and alleviate symptoms:

- Levodopa remains the most effective therapy, especially for bradykinesia and rigidity.

- Dopamine agonists (e.g., pramipexole, ropinirole) are beneficial in early disease or as adjunct therapy.

- MAO-B inhibitors (e.g., rasagiline, selegiline) reduce dopamine breakdown.

- COMT inhibitors (e.g., entacapone) extend levodopa's duration of action.

With disease progression, motor fluctuations and dyskinesias may occur. In carefully selected patients, deep brain stimulation (DBS)—typically targeting the subthalamic nucleus or the globus pallidus internus—provides substantial symptomatic relief.

Social and Economic Impact. PD significantly reduces quality of life, increases caregiver burden, and generates substantial healthcare costs. Optimal patient management requires a multidisciplinary approach involving neurologists, physiotherapists, speech therapists, psychologists, and social support systems.

Conclusion. Modern literature places Parkinson's disease within the broader framework of systemic neurodegeneration. While current therapies effectively control motor symptoms, they do not prevent progression. Future studies must prioritize the identification of reliable biomarkers, clarification of the molecular mechanisms of α-synuclein pathology, and the development of disease-modifying interventions.

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