A Review on Parkinson's Disease

Devprakash Kumar, Sandip Prasad Tiwari*

Faculty of Pharmacy, Kalinga University, Naya Raipur, Chhattisgarh India (492101).

Abstract

This review intends to present an in-depth knowledge about Parkinson's Disease by investigating its etiology, risk factors, pathophysiologic mechanisms, and clinical presentations. The article also discusses diagnostic approaches, such as imaging studies and clinical features, which are pivotal for early and precise diagnosis. Existing treatment strategies, such as pharmacologic drugs like Levodopa, dopamine agonists, MAO-B inhibitors, and deep brain stimulation (DBS), are discussed along with the novel strategies employing gene therapy, stem cell therapy, and nanotechnology-based drug delivery systems.

Keywords: Diagnosis, Existing treatments, Levodopa, dopamine

Introduction

Parkinson's Disease (PD) is a chronic, slowly progressive neurodegenerative disease of the central nervous system (CNS), with major impact on motor function resulting from the degeneration of dopaminergic neurons in the substantia nigra pars compacta, a component of the basal ganglia. This lack of dopamine interferes with normal communication with the striatum, resulting in defective motor control. It was initially described comprehensively in 1817 by British medical Dr. James Parkinson in his "An Essay on the Shaking Palsy." The PD knowledge has evolved over time with dramatic leaps and continues to deepen to reveal complexities well beyond motor dysfunction alone. [1]

According to WHO, neurological conditions like PD rank high among leading causes of disability and premature mortality all over the world. PD now affects more than 10 million people across the globe, with greater prevalence in the elderly. Epidemiological data show that the prevalence of PD

is age-dependent and peaks in the 60–80 year age range. Young-onset Parkinson's Disease (YOPD), however, affecting those under the age of 50, accounts for approximately 5–10% of cases and has its own set of clinical features and issues.

Parkinson’s Disease manifests through a wide range of **motor symptoms** such as:

- **Resting tremor**: rhythmic shaking, often beginning in one hand (e.g., "pill-rolling" tremor),
- **Bradykinesia**: slowness of voluntary movement,
- **Muscle rigidity**: resistance to passive movement,
- **Postural instability**: leading to balance problems and falls.

In addition, PD is increasingly recognized for its **non-motor symptoms**, which may precede motor symptoms by several years. These include:

- **Cognitive decline and dementia**,
- **Mood disorders** (e.g., depression, anxiety),
- **Autonomic dysfunction** (e.g., constipation, urinary incontinence),
- **Sleep disorders** (e.g., REM sleep behavior disorder),
- **Loss of sense of smell (anosmia)**.

These symptoms contribute significantly to morbidity and reduce the **quality of life** for both patients and caregivers.[2]

Keywords: Neurodegenerative, motor function, Basal ganglia, tremor.

Classification

1. Drugs increasing brain dopaminergic system

(a) Dopamine precursor: Levodopa (L-Dopa)

(b) Dopamine agonists. Bromocriptine, pramipexole, ropinirole

(d) Monoamine oxidase (MAO)-B inhibitors: Selegiline (deprenyl), rasagiline

c) NMDA-receptor antagonist (Dopamine facilitator): Amantadine

(e) Catechol-O-methyltransferase (COMT) inhibitors: Tolcapone, entacapone

2. Drugs suppressing brain cholinergic system

(a) Centrally acting anticholinergic drugs. Benztropine, benzhexol (trihexyphenidyl), procyclidine, bipe

(b) Antihistaminics (H:-blockers) with anticholinergic activity: Promethazine, diphenhydramine, orpher.[3]

Pathophysiological Insights and Mechanisms of Parkinson's Disease

The results from studies investigating the **pathophysiology** of PD have provided crucial insights into the **cellular** and **molecular mechanisms** that underpin the disease. This section will discuss the **key findings** in relation to the biological processes involved in PD:

- **Dopaminergic Neuron Degeneration**: One of the core findings of **neuropathological studies** is the **progressive degeneration** of **dopaminergic neurons** in the **substantia nigra**. This degeneration leads to a significant **dopamine deficiency** in the brain, impairing motor function. Studies have demonstrated that the extent of **dopamine loss** correlates with the severity of **motor symptoms**. Furthermore, the **non-motor symptoms** such as **depression** and **cognitive dysfunction** are believed to result from the loss of dopamine in areas outside of the basal ganglia, including the **prefrontal cortex** and **limbic regions**.
- **Alpha-Synuclein Aggregation and Lewy Bodies**: Another critical finding from **molecular studies** is the role of **alpha-synuclein** in the formation of **Lewy bodies**, a hallmark of PD. The aggregation of **misfolded alpha-synuclein** leads to the formation of toxic inclusions that disrupt cellular function. Recent **genetic studies** have shown that **mutations in the SNCA gene**, which encodes alpha-synuclein, increase the likelihood of developing familial forms of PD. Moreover, **post-mortem studies** have shown that **Lewy bodies** accumulate not only in the substantia nigra but also in other brain regions, such as the **cortex** and **limbic system**, contributing to both motor and non-motor symptoms.
- **Mitochondrial Dysfunction**: **Mitochondrial dysfunction** is a central feature of PD pathogenesis. Studies have shown that mitochondrial **complex I** (an enzyme involved in the electron transport chain) is severely impaired in the brains of PD patients. The dysfunction of mitochondria leads to a **reduction in ATP production** and an increase in **reactive oxygen species (ROS)**, which causes **oxidative stress**. This stress damages cellular structures, further exacerbating the degeneration of dopaminergic neurons.

Additionally, research has shown that **mitochondrial dysfunction** contributes to the spread of **alpha-synuclein aggregates** within neurons, amplifying neurodegeneration.

- **Neuroinflammation**: Neuroinflammation has been increasingly recognized as a major contributor to PD progression. Studies have shown that **microglia** (the brain's resident immune cells) are **activated** in PD and release pro-inflammatory cytokines, leading to an environment of **chronic neuroinflammation**. This inflammation exacerbates neuronal injury and accelerates the progression of the disease. **Post-mortem brain tissue** from PD patients shows signs of **microglial activation** and **astrocytosis** in areas affected by neurodegeneration. Recent therapeutic trials have also explored **anti-inflammatory drugs** as potential treatment options for PD, showing some promise in slowing disease progression.
- **Genetic Factors**: The identification of **genetic mutations** associated with PD has led to a deeper understanding of the disease's pathogenesis. **Mutations in the LRRK2 gene** have been linked to **autosomal dominant forms of PD**, while mutations in **PINK1**, **DJ-1**, and **parkin** are associated with **early-onset familial PD**. However, most PD cases are **idiopathic**, meaning they have no identifiable genetic cause. Genetic studies suggest that **genetic susceptibility** may interact with environmental factors to increase the risk of developing PD.[4]

Keywords: Astrocytocis, dopamine deficiency, neuroinflammation.

1. Etiology and Pathogenesis

1.1 Genetic Contributions

Although Parkinson's Disease is primarily sporadic, about 10–15% of cases are familial and can be attributed to specific genetic mutations. Genome-wide association studies (GWAS) and whole-exome sequencing have identified numerous genes implicated in PD, such as:

- **SNCA (alpha-synuclein):** Point mutations and gene duplication/triplication lead to early-onset PD.
- **LRRK2 (Leucine-rich repeat kinase 2):** The most common cause of familial PD; G2019S mutation is well studied.

- **PINK1, PARKIN, DJ-1:** Involved in mitochondrial quality control and oxidative stress regulation.

A landmark study by **Nalls et al. (2019)** reported over 90 genetic loci associated with PD susceptibility, emphasizing the role of both rare and common variants.

1.2 Alpha-Synuclein Pathology

Alpha-synuclein, a presynaptic neuronal protein, aggregates into **Lewy bodies**, which are considered pathological hallmarks of PD. Studies by **Spillantini et al. (1998)** confirmed its central role in neuronal toxicity. The prion-like behavior of misfolded alpha-synuclein—spreading from neuron to neuron—is supported by both in vitro and in vivo models, suggesting a possible mechanism for disease progression.

1.3 Mitochondrial Dysfunction and Oxidative Stress

Numerous studies have documented mitochondrial respiratory chain defects, particularly **complex I deficiency**, in PD patients. This impairs ATP production and increases the generation of **reactive oxygen species (ROS)**, leading to oxidative damage and apoptosis. The **PINK1-Parkin** pathway has been shown to play a crucial role in mitophagy, and mutations in these genes contribute to dysfunctional mitochondrial clearance.

1.4 Neuroinflammation

Activated **microglia** and elevated levels of pro-inflammatory cytokines (e.g., IL-1β, TNF-α) have been observed in the substantia nigra of PD brains. Chronic neuroinflammation, as discussed by **Hirsch et al. (2020)**, exacerbates neurodegeneration and presents a potential target for disease-modifying therapy. [5]

2. Clinical Spectrum and Diagnostic Approaches

2.1 Motor Symptoms

Classic motor features include:

- **Tremor at rest** (commonly "pill-rolling")

- **Bradykinesia** (slowness of movement)
- **Muscle rigidity**
- **Postural instability**

These symptoms are usually asymmetrical in early stages and become bilateral with disease progression. The **Hoehn and Yahr staging scale** remains widely used for grading motor severity.

2.2 Non-Motor Symptoms

A growing body of literature has emphasized the importance of non-motor features, which can precede motor symptoms by decades:

- **Cognitive impairment and dementia**
- **Mood disorders:** depression, anxiety
- **Autonomic dysfunction:** orthostatic hypotension, constipation
- **REM Sleep Behavior Disorder (RBD)**

These symptoms significantly reduce quality of life and are now integral to diagnosis and management strategies.

2.3 Diagnostic Tools

- **Clinical Diagnosis:** Based on the MDS Clinical Diagnostic Criteria.
- **Neuroimaging:** DAT-SPECT imaging confirms dopaminergic deficit; MRI can rule out mimicking conditions.
- **Biomarkers:** Research is ongoing into CSF alpha-synuclein levels, neurofilament light chain (NFL), and blood exosomal markers.

3.0 Treatment Modalities

3.1 Pharmacotherapy

Levodopa, in combination with **carbidopa**, remains the most effective treatment for motor symptoms. However, chronic use results in **motor complications**:

- Wearing-off phenomenon
- Peak-dose dyskinesias

Other medications include:

- **Dopamine agonists**: Less effective but useful in early stages (e.g., pramipexole)
- **MAO-B inhibitors**: Delay levodopa initiation (e.g., rasagiline)

- **COMT inhibitors**: Extend levodopa half-life

3.2 Surgical Interventions

Deep Brain Stimulation (DBS) has been shown to improve motor function and reduce medication burden. The **subthalamic nucleus (STN)** and **globus pallidus interna (GPi)** are primary targets. Patient selection is critical—ideal candidates are those with levodopa-responsive symptoms but experiencing motor fluctuations.

3.3 Adjunctive Therapies

Emerging interventions:

- **Focused Ultrasound (FUS)** for tremor
- **Continuous dopaminergic delivery** via infusion pumps (apomorphine or levodopa gel)

Non-medical therapies:

- **Physical therapy**, **speech therapy**, **occupational therapy**
- **Music and dance therapy** to improve motor coordination and mood
- **Mindfulness** and **CBT** for neuropsychiatric symptoms

4.0 Advances in Research and Novel Therapies

4.1 Disease-Modifying Therapies

- **Immunotherapy**: Monoclonal antibodies against alpha-synuclein (e.g., prasinezumab) are in clinical trials.
- **Gene therapy**: Viral vectors delivering GAD or neurotrophic factors like **GDNF** are under investigation.
- **Antioxidants** and **anti-inflammatory agents**: Coenzyme Q10, NSAIDs, and natural compounds like curcumin are being tested.[6]

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