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# REVIEWING PARKINSON'S DISEASE: INSIGHTS AND PERSPECTIVES

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## ABSTRACT
Parkinson's disease (PD) is a neurodegenerative disorder that typically appears between the ages of 55 and 65. It presents both motor and non-motor symptoms that progressively worsen, significantly affecting an individual's quality of life. While a cure for PD has yet to be found, various treatments are available to help manage its symptoms. The field of PD management is advancing, aiming to develop new and improved treatment methods. Physicians can now tackle patient-specific concerns as they arise, alongside the primary motor symptoms of PD, using pharmaceutical, surgical, and therapeutic interventions. This study explores current and validated treatment options for Parkinson's disease (PD) that offer personalized care and reduce side effects associated with conventional medications.

**Keywords:** Parkinson’s disease, Parkinson’s treatment, substantia nigra, basal ganglia, Lewy bodies, α-synuclein, dopamine, levodopa

## INTRODUCTION
In 1817, Dr. James Parkinson first described Parkinson's disease (PD) as a "shaking palsy." This neurodegenerative disorder progresses over time, presenting both motor and non-motor symptoms. The gradual degeneration impacts muscular control and movement, significantly affecting patients, their families, and caregivers. The loss of striatal dopaminergic neurons leads to PD's motor symptoms, while non-motor symptoms indicate neuronal loss in nondopaminergic regions [1]. The motor characteristics, such as bradykinesia, muscle stiffness, and resting tremor, are collectively known as Parkinsonism. Although PD is the most common cause of Parkinsonism, other conditions and drug-induced causes can also produce similar symptoms[2].

Studies suggest that the pathophysiological changes associated with PD may precede motor symptoms, including non-motor manifestations like depression, sleep disturbances, and cognitive impairments. This preclinical period has driven research into protective or preventive medicines [3]. PD is one of the most prevalent neurological disorders, affecting about one million Americans according to the Parkinson's Disease Foundation. In the United States, there are roughly 20 new cases per 100,000 people annually, totaling around 60,000

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new cases each year, with an average onset age of over 60. The prevalence increases from 1% in those over 60 to 1% to 3% in those over 80, though these numbers likely underestimate undiagnosed cases [4].

While PD predominantly affects the elderly, individuals in their 30s and 40s can also be diagnosed. The incidence of PD is higher in males, with a 3:2 ratio compared to females. This difference is thought to be due to the neuroprotective effects of estrogen on the nigrostriatal dopaminergic pathway, which may delay onset in females. The unpredictable but significant progression of PD profoundly impacts individuals, families, and communities, with advanced stages potentially leading to severe complications such as pneumonia, which can be fatal [5].

Current treatments aim to manage symptoms. Research suggests that a multidisciplinary care team, including movement disorder specialists, social workers, pharmacists, and other medical professionals, can benefit PD patients. Various genetic abnormalities and risk factors are associated with PD, including free radical production, oxidative stress, and environmental pollutants [6].

| **Risk Factors associated with Parkinson Disease** | |
|---|---|
| 1. | Elevated cholesterol |
| 2. | Environmental toxins |
| a) | Carbon disulfide |
| b) | Cyanide |
| c) | Herbicides |
| d) | Methanol and organic solvents |
| e) | Pesticides |
| 3. | Head trauma |
| 4. | High caloric intake |
| 5. | Increased body mass index |
| 6. | Inflammation associated with activation of microglia |
| 7. | Methcathinone (manganese content) |
| 8. | Methamphetamine/amphetamine abuse |
| 9. | Mitochondrial dysfunction |
| 10. | Nitric oxide toxicity |
| 11. | Oxidative stress |
| a) | Formation of free radicals (e.g., hydrogen peroxide) |
| b) | Potent neurotoxins (e.g., 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) |
| 12. | Post-infection states |
| 13. | Signal-mediated apoptosis |

Table – 1: Risk Factors associated with Parkinson's Disease

There is no evidence to establish genetic links between PD and some gene alterations (Table 2. Interestingly, there is a negative correlation between coffee consumption, cigarette smoking, and the risk of developing Parkinson's disease. The beneficial effects of coffee may be due to its action as an adenosine antagonist, while the protective effects of smoking could be related to the inhibition of the enzyme monoamine oxidase (MAO. The varying global prevalence of Parkinson's disease (PD) suggests that genetic, environmental, and ethnic factors all play a role in its pathophysiology. Ongoing research into the biomedical aspects of

Parkinson's disease (PD) may lead to the identification of new risk factors and future therapeutic and preventative options[7].

| Gene Mutations Associated With Parkinson's Disease |
|---|
| • Alpha-synuclein gene (SNCA) |
| • Eukaryotic translation initiation factor 4 gamma 1 gene (EIF4G1) |
| • Glucocerebrosidase gene (GBA) |
| • Leucine-rich repeat kinase 2 (LRRK2) gene loci |
| • PTEN-induced putative kinase 1 (PINK1) gene loci |
| • Superoxide dismutase 2 gene (SOD2) |
| • Vacuolar protein sorting 35 homolog gene (VPS35) |

Table – 2: Gene Mutations Associated With Parkinson's disease

**Pathophysiology**

Parkinson's disease (PD) affects the extrapyramidal system, including the basal ganglia motor structures. It is characterized by a decline in motor function due to the loss of dopaminergic activity, which drives the clinical features of the disease. The presence of non-motor symptoms indicates the involvement of other neurotransmitter systems, including glutamatergic, cholinergic, serotonergic, and adrenergic, as well as neuromodulators like adenosine and enkephalins[8]. Research from the late 1950s identified striatal dopamine depletion as the primary cause of PD's motor symptoms. Further evidence suggests that PD may begin in the anterior olfactory nucleus, the dorsal motor nucleus of the vagal and glossopharyngeal nerves, or the brainstem, following a progression from the brainstem to higher cortical levels. Histological features of PD include Lewy bodies (LBs) and the loss of pigmented dopaminergic neurons[9].

In PD, the progressive degeneration of dopaminergic neurons in the substantia nigra pars compacta (SNpc), which project to the striatum (nigrostriatal pathway), leads to the loss of dopaminergic function[10]. Motor symptoms typically manifest after 50% to 80% of these neurons are destroyed, indicating a compensatory mechanism in the early stages of the disease. Dopamine receptors D1 (excitatory) and D2 (inhibitory) influence motor activity within the extrapyramidal system, which includes the substantia nigra pars reticulata (SNpr) and the basal ganglia's internal globus pallidus segment (GPi). These components are part of larger circuits involving the cortex and thalamus[11].

In PD patients, dopamine depletion in the striatum results in increased activity in the GPi/SNpr circuits, causing gamma-aminobutyric acid (GABA) dysfunction and inhibiting the thalamus. This ultimately reduces the thalamus's ability to stimulate the frontal cortex, leading to the diminished motor activity characteristic of Parkinson's disease[12].

**Pathophysiology**

Clinical improvement in the motor symptoms of Parkinson's disease (PD) is achieved by restoring dopamine activity in the striatum through the activation of D2 and D1 receptors using dopaminergic treatments. The depletion of dopamine also leads to increased cholinergic activity and reduced thalamic activation due to the loss of dopamine's inhibitory effect

 

Ongoing research continues to support the idea that PD is characterized by multiple levels of diffuse global network failure within the neurological system.

A key histological feature of PD is the presence of Lewy bodies (LBs), [13]which are internal cytoplasmic aggregates composed of proteins, lipids, and other components. LBs are important indicators of long-term neurodegenerative diseases, including PD. These spherical bodies with radiating fibrils are found in the dopaminergic neurons of the substantia nigra in PD patient. Research suggests that refractory proteolytic processes involving abnormal protein breakdown or overproduction, influenced by genetic mutations, may contribute to LB formation. Mutations in the alpha-synuclein (αSyn) gene have been observed to aggregate and form insoluble fibrils associated with LBs. Future PD treatments may target αSyn protein.

The overproduction of misfolded ubiquitin proteins, which play a crucial role in protein recycling, also contributes to LB formation. Dysfunction of the ubiquitin-proteasome system (UPS) is a secondary cause of the accumulation of these proteins. Different lesion patterns are observed at various stages of PD, suggesting that LB formation may contribute to the neurodegeneration characteristic of the disease. Early (premotor) symptoms, including olfactory and rapid eye movement (REM) disturbances, may be linked to lesions in the dorsal nucleus, medulla, and pons. The motor symptoms of PD are partly due to lesions in the nigrostriatal region later in the disease. LBs are also associated with the dementia seen in Parkinson's disease (PD), similar to their presence in individuals with dementia with Lewy bodies (DLB). However, PD and DLB have distinct clinical presentations, with motor symptoms appearing earlier and more prominently in PD. While amyloid beta 1-42 is primarily linked to the pathophysiology of Alzheimer's disease (AD), recent research suggests that the presence of this biomarker in cerebrospinal fluid may also predict cognitive impairment in PD. These findings align with other studies indicating that AD pathology exacerbates cognitive impairment in PD and may help forecast cognitive decline associated with the disease.

**Studies on Inflammation and Diagnosis**

Research is also exploring the role of inflammation, particularly cytokines and other mediators, in the etiology of Parkinson's disease (PD). The pathophysiology of PD may involve inflammatory responses triggered by the loss of dopaminergic neurons. In vitro studies have confirmed the activation of astrocytes and microglia following damage to dopaminergic neurons.

In conclusion, multiple molecular pathways are involved in PD, a complex neurodegenerative disease that contributes to its neuropathophysiology.

**Diagnosis**

A thorough history and physical examination are essential for the differential diagnosis of Parkinson's disease (PD). Challenging or uncertain cases should be referred to a movement disorder specialist for further evaluation. Since there are no definitive tests for PD, diagnosis must be clinical. Physicians diagnose PD by reviewing the patient's medical history,

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evaluating symptoms, and ruling out other potential diagnoses such as multiple-system atrophy, dementia with Lewy bodies (DLB), and essential tremor (Table 3).

| |
|---|
| Alzheimer's disease |
| Basal ganglia tumor |
| Benign essential tremor |
| Cerebrovascular disease |
| Corticobasal degeneration |
| Creutzfeldt–Jakob disease |
| Dementia with Lewy bodies |
| Drug-induced parkinsonism |
| Metabolic causes (e.g., hypoparathyroidism, thyroid dysfunction, nutritional deficiencies) |
| Multiple-system atrophy |
| Normal-pressure hydrocephalus |
| Olfactory dysfunction |
| Olivopontocerebellar atrophy |
| Post-traumatic brain injury Parkinson's disease |
| Progressive supranuclear palsy |
| Shy–Drager syndrome |
| Subdural hematoma |
| Wilson's disease |

**Table - 3: Diseases and Conditions That May Require Differentiation From Parkinson's Disease**

**The Classical Triad and Clinical Presentation**

The "classical triad" of Parkinson's disease (PD) consists of three main motor characteristics: a 4-Hz to 6-Hz resting tremor, "cogwheel" rigidity, and bradykinesia (Table 4). These key features are often the initial clinical signs of the disease. Additionally, about 50% of PD patients develop postural instability as a fourth symptom within five years of diagnosis. Although PD is generally associated with the elderly, younger individuals can also be affected, particularly those with specific genetic variations. Clinically, younger patients (under 60 years old) may present with less bradykinesia and rigidity, potentially leading to a missed or delayed diagnosis.

**Differential Diagnosis and Similar Conditions**

Identifying illnesses with symptoms resembling Parkinson's disease (PD) is a crucial step in the diagnostic process. Table 3 lists several conditions that should be considered in the differential diagnosis, requiring additional testing to rule them out. For example, benign essential tremor often appears as an intention-type tremor, which occurs with movement and involves a greater degree of head involvement. Patients with dementia with Lewy bodies (DLB) may exhibit PD-like symptoms along with cognitive changes and visual hallucination. Movement disorder specialists may be needed to confirm the diagnosis, as many other illnesses can mimic PD.

In cases where the patient's history suggests possible exposure to certain factors, laboratory tests may be necessary to rule out nutritional deficiencies and other anomalies, such as thyroid disease. Measuring plasma levels of ceruloplasmin and copper may also be needed to rule out Wilson's disease. Additional diagnostic techniques include levodopa or apomorphine bedside dopaminergic challenge tests, though some neurology professionals oppose their use. Neuropsychiatric tests, sleep studies, and visual examinations may also be useful, especially for visual abnormalities like abnormal color vision, which can result from altered intraretinal dopaminergic transmission.

Since drug-induced parkinsonism (DIP) is one of the few reversible causes of PD, it should be considered in the differential diagnosis. Therefore, a thorough medication review is

 

essential for all patients suspected of having PD to avoid misdiagnosis. At-risk populations for DIP include patients with various comorbidities, older women, and those taking multiple medications at high doses for extended periods.

Medications most frequently associated with DIP include dopamine receptor inhibitors such as risperidone, thiothixene, and haloperidol. If antipsychotic medications are needed for PD patients, those with a lower risk of DIP, such as quetiapine and clozapine, are recommended. Other drugs linked to DIP include the gastrointestinal prokinetic metoclopramide and antiemetics with a phenothiazine core, such as prochlorperazine and promethazine. Numerous other medications, including antidepressants, lithium, anticonvulsants, and certain antihypertensives like methyldopa and calcium-channel blockers, can also cause DIP. Managing DIP involves identifying and discontinuing the contributing medication(s), which typically resolves the symptoms, although in some cases, they may persist for several months or even a year or two .

**Discussion**

Parkinson's disease (PD) is a progressive, long-term neurological disorder characterized by both motor and nonmotor symptoms. The primary cause of the motor symptoms, including bradykinesia, "cogwheel" rigidity, and resting tremor, is the depletion of striatal dopamine. Nonmotor symptoms include cognitive changes, depression, and sleep disturbances.

A thorough history and physical examination are essential components of the differential diagnosis for PD. Identifying illnesses with symptoms similar to PD is crucial in the diagnostic process. There are no definitive tests to confirm a PD diagnosis. The most widely used scale for assessing the clinical status of individuals with PD is the Unified Parkinson's Disease Rating Scale (UPDRS).

The primary goal of PD management is to treat the symptomatic motor and nonmotor aspects of the disease to improve the patient's overall quality of life. Currently, no therapies have been found to slow the progression of the disease or provide a neuroprotective effect.

**Conclusion**

Nonmotor symptoms are commonly identified in Parkinson's disease (PD), a neurodegenerative disorder primarily diagnosed based on its motor aspects. While the exact cause remains unknown, it is believed to result from a combination of environmental and genetic risk factors, with sex and age being significant contributors. Factors such as the intensity of parkinsonism, rate of progression, response to levodopa, early gait abnormalities, and symmetry of parkinsonism may increase the risk of higher mortality. It is crucial to recognize the potential for misdiagnosing idiopathic PD as Parkinson-plus syndrome during differential diagnosis. Although neuroprotective treatments are not yet available, numerous medical and surgical therapies can manage both motor and nonmotor symptoms at various stages of the disease. Ongoing trials for new medications suggest that better treatment options may soon be available.

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