

STUDY ON PARKINSON'S DISEASE AND PARKINSON-PLUS SYNDROMES

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Abstract

Parkinson's disease (PD) is a progressive neurodegenerative disorder caused by the loss of dopamine-producing neurons in the substantia nigra, leading to disrupted signaling in the basal ganglia. This results in motor symptoms such as resting tremor, bradykinesia, rigidity, and postural instability, as well as non-motor symptoms including cognitive decline, mood disorders, sleep disturbances, and autonomic dysfunction. Symptoms typically progress gradually and often respond initially to dopaminergic medications like Levodopa.

Parkinson-plus syndromes, or atypical Parkinsonism, include disorders such as multiple system atrophy, progressive supranuclear palsy, corticobasal degeneration, and dementia with Lewy bodies. These conditions share Parkinson-like motor features but progress more rapidly and often present additional neurological signs, including early cognitive impairment, autonomic failure, gaze abnormalities, and speech or swallowing difficulties. Response to dopaminergic therapy is generally poor, making management more challenging. Accurate differentiation between PD and Parkinson-plus syndromes is essential for prognosis, treatment planning, and optimizing quality of life.

Keywords: *Parkinson's disease, Parkinson-plus syndrome, Dopamine, Basal ganglia, Neurodegenerative disorders*

Introduction

Parkinson's disease (PD) is a chronic [1], progressive neurodegenerative disorder that primarily affects movement

and motor control. It is characterized by the gradual loss of dopamine-producing neurons in the substantia nigra, a critical region of the midbrain that plays a central role in regulating smooth, coordinated muscle movements. Dopamine is a key neurotransmitter that facilitates communication between nerve cells in the brain, particularly in pathways connecting the substantia nigra to the basal ganglia, which are essential for initiating and controlling voluntary movements[2]. The deficiency of dopamine in PD disrupts these pathways, leading to the hallmark motor impairments of the disease.

The onset of Parkinson's disease [3] is typically subtle and progressive. Early motor symptoms often include resting tremor, usually beginning in one hand or limb, muscle rigidity, bradykinesia (slowness of movement), and postural instability. Tremors [4] are most noticeable when the affected limb is at rest and may diminish during voluntary movement. Muscle rigidity results in stiffness and reduced range of motion, which can cause discomfort and interfere with daily activities. Bradykinesia manifests [5] as slowness in initiating and performing movements, making tasks such as walking, dressing, and writing increasingly difficult. Postural instability,

which usually develops in the later stages of the disease, increases the risk of falls and contributes significantly to disability. These motor symptoms collectively reduce an individual's independence and significantly impact quality of life.

Beyond motor impairments[6], Parkinson's disease is associated with a broad spectrum of non-motor symptoms, which are increasingly recognized as significant contributors to patient morbidity. Non-motor manifestations include cognitive decline, depression, anxiety, sleep disturbances, fatigue, and autonomic dysfunction, such as orthostatic hypotension, constipation, and urinary problems. Some non-motor symptoms may appear years before motor signs, making early diagnosis challenging. Cognitive impairment can range from mild executive dysfunction to dementia in the later stages, while mood disturbances such as depression and anxiety further exacerbate functional limitations. Sleep disorders, including restless leg syndrome and REM [7] sleep behavior disorder, are common and can significantly affect overall well-being.

The etiology of Parkinson's disease remains incompletely understood but is believed to involve a complex interplay of genetic, environmental, and age-related factors. While the majority of cases are sporadic, approximately 10–15% of patients have a familial form linked to mutations in genes such as SNCA, LRRK2, PARK2, and PARK7 [8]. Environmental exposures, including pesticides, herbicides, heavy metals, and

repeated head trauma, have also been implicated in increasing the risk of PD. Aging remains the most significant risk factor, with the prevalence of Parkinson's disease increasing sharply after the age of 60. Early-onset Parkinson's disease, which occurs before age 50, is rare but may be associated with stronger genetic influences.

Although there is currently no cure for Parkinson's disease [9], multiple therapeutic strategies aim to alleviate symptoms and improve patients' quality of life. Pharmacological interventions focus on restoring or mimicking dopamine function. **Levodopa**[10], the most effective therapy, is converted to dopamine in the brain and significantly improves motor symptoms. **Dopamine agonists** and **monoamine oxidase B (MAO-B) inhibitors** also enhance dopaminergic activity [11] and can be used alone or in combination with levodopa. For patients who do not respond adequately to medications or who develop motor complications, surgical interventions such as **deep brain stimulation (DBS)** may be considered. Complementary approaches including **physical therapy, occupational therapy, and speech therapy** play a vital role in maintaining mobility, coordination, communication, and independence. Multidisciplinary care is essential to address both motor and non-motor symptoms effectively.

Parkinson-plus syndromes, also referred to as atypical Parkinsonism [12], comprise a group of rare

neurodegenerative disorders that share clinical features with Parkinson's disease but differ in underlying pathology, disease progression, and response to treatment. While these disorders also involve movement impairments, they often present additional neurological symptoms that are uncommon in idiopathic PD, such as early cognitive decline, autonomic dysfunction, speech and swallowing difficulties, and abnormal eye movements. Parkinson-plus syndromes [13] typically progress more rapidly than Parkinson's disease and respond poorly to standard dopaminergic therapies like levodopa, making management more challenging.

The major types of Parkinson-plus syndromes include **Multiple System Atrophy (MSA)**, **Progressive Supranuclear Palsy (PSP)**, **Corticobasal Degeneration (CBD)**, and **Lewy Body Dementia (LBD)** [14]. Each disorder is associated with abnormal accumulation of specific proteins in the brain, which disrupt normal neuronal function. MSA and LBD are linked to alpha-synuclein accumulation, whereas PSP and CBD are associated with tau protein pathology. These proteinopathies target distinct regions of the brain involved in motor control, cognition, and autonomic function. For example, MSA primarily affects the basal ganglia, cerebellum, and autonomic nervous system, leading to movement difficulties, balance problems, and autonomic dysfunction. PSP predominantly affects the brainstem, frontal lobe, and basal ganglia, resulting in impaired eye movements, early falls,

and cognitive deficits. CBD [15] involves the basal ganglia and cerebral cortex, causing asymmetrical movement, limb rigidity, and cognitive impairment, while LBD affects the basal ganglia, cerebral cortex, and occipital lobe, leading to dementia, hallucinations, and movement disorders.

Accurate diagnosis of Parkinson-plus syndromes is crucial for prognosis, treatment planning, and patient counseling. Misdiagnosis can delay appropriate interventions and affect outcomes. Unlike idiopathic PD, these syndromes often require a **multidisciplinary approach** that combines symptomatic management, supportive therapies, and careful monitoring of disease progression. Understanding the clinical features, underlying pathology, and affected brain regions of both Parkinson's disease and Parkinson-plus syndromes [16] is essential for clinicians, researchers, and caregivers to optimize patient care, improve quality of life, and advance research into more effective treatments.

Living with Parkinson's and Parkinson's plus disease requires a multidisciplinary approach and long-term care. Support from healthcare professionals, caregivers, and family members is essential to help individuals cope with the physical, emotional, and social challenges posed by the condition. Ongoing research continues to explore new treatments and potential disease-modifying therapies, offering hope for improved outcomes and, ultimately, a cure in the future.

Symptoms for Parkinson Disease

The below diagram shows how dopamine from Pars Compacta regulates movement [17] through the basal ganglia, and Pars Reticulata sends

inhibitory signals to the thalamus to control posture, eye movement, and muscle activity and is shown in Figure 1 and other details are listed in Table 1

Table 1 Major Motor and Non-Motor Symptoms of Parkinson’s Disease and the Primary Brain Regions Affected

Motor Symptoms	Non-Motor Symptoms	Affected Brain Regions
- Resting Tremor - Muscle Rigidity - Bradykinesia (Slowed movements) - Postural Instability	- Cognitive Impairment - Mood Disorders - Sleep Disturbances - Loss of Smell	- Substantia Nigra - Basal Ganglia - Subthalamic Nucleus - Thalamus

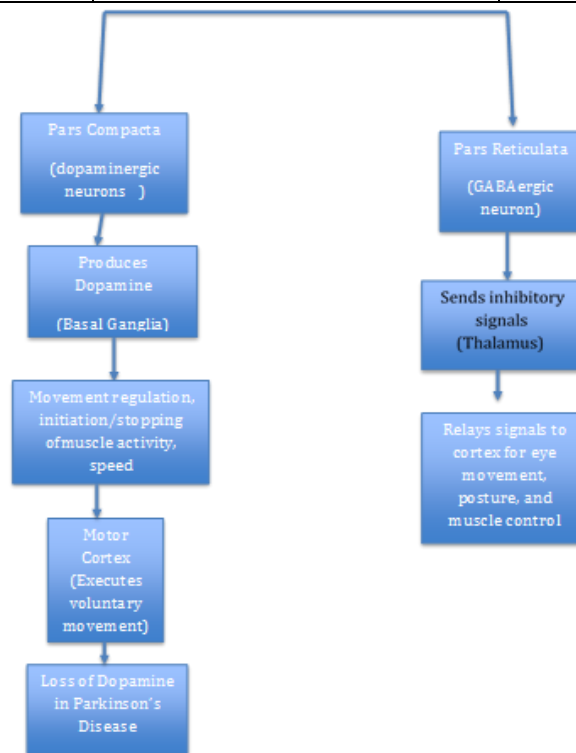


Figure 1. Diagram illustrating the role of the substantia nigra in motor control

Dopamine produced in the substantia nigra is essential for the regulation of voluntary movement through its action on the basal ganglia. Loss of this neurotransmitter disrupts motor control, resulting in tremors, rigidity, and slowed

movements. Understanding the role of dopamine in movement regulation is fundamental to understanding movement disorders such as Parkinson’s disease and remains a key focus of neurological research and treatment development.

Parkinson-Plus Syndromes Parkinson-plus syndromes are atypical Parkinsonian disorders characterized by additional neurological symptoms and faster disease progression.

Symptoms for Parkinson-Plus

The summary of the four major Parkinson-plus syndromes and their key symptoms [18] are listed below in Table 2.

Table 2. Summary of the four major Parkinson-plus syndromes – MSA, PSP, CBD, and LBD – highlighting their characteristic motor, non-motor, and cognitive symptoms

Disorder	Key Symptoms	Protein Involved	Affected Brain Areas
Multiple System Atrophy (MSA)	Autonomic dysfunctions (blood pressure drops, sweating, breathing issues), early bladder problems (frequent urination, urgency, incomplete emptying), balance problems, frequent falls, speech difficulties	Alpha-synuclein	Basal ganglia, cerebellum, autonomic nervous system
Progressive Supranuclear Palsy (PSP)	Eye movement problems (difficulty looking up/down, blurred or double vision), early falls, unsteady walking, speech difficulties	Tau protein	Brainstem, frontal lobe, basal ganglia
Corticobasal Degeneration (CBD)	Asymmetrical movement (one-sided limb difficulties), limb stiffness/rigidity, cognitive impairment (thinking, memory, decision-making)	Tau protein	Cerebral cortex, basal ganglia
Lewy Body Dementia (LBD)	Early dementia (memory loss, confusion), visual hallucinations, movement problems, behavioral changes	Alpha-synuclein (Lewy bodies)	Cerebral cortex, basal ganglia, occipital lobe

Parkinson-plus syndromes – MSA, PSP, CBD, and LBD – are characterized by overlapping motor symptoms with additional cognitive, autonomic, and sensory impairments. Each disorder involves abnormal protein accumulation, specific brain region damage, and unique symptom patterns, making accurate

diagnosis essential for prognosis, management, and patient care.

Parkinson-Plus Syndromes: Activity Patterns, White Matter, and Affected Body Systems

Patients with Parkinson-plus syndromes often exhibit fluctuations in activity levels throughout the day. **In the**

morning, they tend to be more active. After a night of rest, the brain is refreshed, energy levels are higher, and dopamine levels are relatively better. This reduces muscle stiffness, allowing patients to move more freely. Mentally, they feel sharper and more alert, often using this time to perform important daily tasks or engage in physical activity.

White matter [19] is a critical component of the central nervous system, composed primarily of myelinated axons that facilitate rapid transmission of electrical signals between different brain and spinal cord regions. White matter enables communication between grey matter areas, ensuring smooth coordination of motor and cognitive functions. In the **cerebrum**, white matter forms the inner layer beneath the cerebral cortex. In the **cerebellum**, it lies beneath the grey matter in a branching structure called the arbor vitae, which coordinates balance and movement. The **brainstem**, including the midbrain, pons, and medulla, contains white matter tracts essential for motor control and sensory processing, connecting the brain to the spinal cord. Pathologies affecting white matter, such as **demyelinating diseases** like multiple sclerosis, disrupt signal transmission, causing muscle weakness, vision problems, and cognitive decline.

In the evening or at night, Parkinson-plus patients are usually less active. Dopamine levels drop, muscles become stiff and fatigued, and the brain experiences mental exhaustion. This results in slower movements,

drowsiness, confusion, and overall inactivity. Patients may appear quiet, withdrawn, or nearly motionless by night.

Multiple body systems are affected in Parkinson-plus syndromes, reflecting the widespread impact of the brain pathology:

1. **Brain** – As the main control center, damage to the brain disrupts all downstream body functions.
2. **Autonomic nervous system** – Especially affected in Multiple System Atrophy (MSA), it regulates involuntary functions such as heart rate, blood pressure, digestion, and bladder control. Symptoms include dizziness due to sudden blood pressure drops, urinary urgency or incontinence, constipation, and impaired sweating or temperature regulation.
3. **Heart and blood vessels** – Autonomic dysfunction can cause irregular heartbeat, fainting, and low blood pressure.
4. **Muscles and movement system** – Abnormal brain signals lead to stiffness, abnormal postures (e.g., neck tilting in PSP, twisted limbs in CBD), difficulty swallowing (dysphagia), impaired eye movements (especially in PSP), and slurred or soft speech.
5. **Speech and swallowing organs** – Tongue, throat, and voice box muscles are affected, causing slurred speech, soft voice, and chewing or

swallowing difficulties, which can lead to choking or weight loss.

6. **Lungs and breathing** – Weakened muscles in advanced stages may impair breathing, and swallowing problems can cause aspiration of food into the lungs.
7. **Posture and balance systems** – Disrupted brain signals to core, leg, and spine muscles cause freezing of gait, difficulty standing, and frequent falls.

Heart Problems in Parkinson-Plus Diseases

In Parkinson-plus disorders, such as Multiple System Atrophy (MSA) and Progressive Supranuclear Palsy (PSP) [20], the brain regions that control the autonomic nervous system are damaged. Since this system regulates the heart's automatic functions, patients may develop cardiovascular complications. Common issues include **orthostatic hypotension**, a sudden drop in blood pressure upon standing that can cause dizziness or fainting, irregular heartbeats, and poor heart rate control. Reduced blood flow to the brain can lead to fatigue, weakness, and, in rare cases, life-threatening heart events.

Lung Issues in Parkinson-Plus Diseases

Breathing is normally controlled automatically by the brainstem. In Parkinson-plus diseases, this control may weaken, especially when the brainstem is affected. As a result, **breathing muscles become weak**, leading to shallow or slow

breathing [21]. The cough reflex is often impaired, making it difficult to clear mucus. This increases the risk of **aspiration**, where food or liquids enter the lungs, potentially causing aspiration pneumonia. Patients may experience shortness of breath, coughing during meals, or recurrent lung infections.

Digestive Problems in Parkinson-Plus Diseases

The digestive system communicates [22] with the brain through the autonomic nervous system. When this pathway is disrupted, digestion slows, causing **constipation, delayed stomach emptying (gastroparesis), difficulty swallowing, early satiety, and, in severe cases, malnutrition or weight loss**. These issues significantly affect daily life and often require dietary adjustments or medical management.

Esophagus Problems in Parkinson-Plus Diseases

The esophagus, responsible for transporting food from the mouth to the stomach, relies on both voluntary and involuntary muscles [23]. Parkinson-plus patients may experience **dysphagia (difficulty swallowing), food sticking in the throat or chest, choking, aspiration, and weight loss**. Speech and swallowing therapists play a vital role in helping patients safely eat through specialized techniques, diet modifications, and exercises to improve swallowing function.

Diagnosis

The diagnosis of neurological disorders, particularly movement disorders such as Parkinson's disease, relies on a combination of clinical evaluation and advanced imaging and laboratory techniques. Because there is no single definitive test, diagnosis includes a detailed neurological examination supported by imaging studies such as MRI, functional scans like DAT scans, SPECT, and PET, as well as cerebrospinal fluid (CSF) analysis [24]. Together, these tools help clinicians confirm the diagnosis, rule out other conditions, and assess disease progression.

A neurological examination is the first and most essential step in the diagnostic process. During this assessment, a neurologist evaluates motor function, muscle tone, reflexes, coordination, gait, posture, and balance. Key features such as resting tremor, rigidity, bradykinesia, and postural instability are carefully observed. The physician also assesses speech, facial expression, and handwriting, which may show subtle changes. In addition to motor symptoms, cognitive function, mood, and autonomic symptoms are evaluated, as non-motor features can provide important diagnostic clues. A thorough medical history, including symptom onset, progression, family history, and medication use, further supports clinical judgment.

Magnetic Resonance Imaging (MRI) is commonly used to exclude other

neurological conditions that may mimic symptoms. While MRI does not directly diagnose Parkinson's disease, it helps rule out structural abnormalities such as brain tumors, strokes, multiple sclerosis, or normal pressure hydrocephalus. Advanced MRI techniques may reveal subtle changes in brain structures, including the substantia nigra, but these findings are mainly supportive rather than diagnostic. MRI is particularly valuable in atypical or early cases where symptoms are unclear.

A dopamine transporter (DAT) scan is a specialized imaging technique that plays a significant role in diagnosing dopaminergic disorders. This scan uses a radioactive tracer to visualize dopamine transporter activity in the brain. Reduced uptake in the basal ganglia suggests loss of dopamine-producing neurons, supporting a diagnosis of Parkinson's disease or related conditions. DAT scans are especially useful in differentiating Parkinson's disease from essential tremor or drug-induced movement disorders.

Single Photon Emission Computed Tomography (SPECT) and Positron Emission Tomography (PET) scans provide functional imaging of brain activity and neurotransmitter systems. SPECT imaging, often used in DAT scans, helps assess dopamine function and blood flow in the brain. PET scans offer more detailed metabolic and molecular information, allowing visualization of glucose metabolism or dopamine synthesis. These scans are primarily used in research settings or complex cases, as

they are expensive and not always widely available.

Cerebrospinal fluid (CSF) analysis can provide valuable biochemical information. CSF is obtained through a lumbar puncture and analyzed for biomarkers that may indicate neurodegeneration or rule out infections, inflammatory disorders, or other neurological diseases. While CSF analysis is not routinely used for Parkinson's disease diagnosis, ongoing research aims to identify specific biomarkers that could aid in early detection and disease monitoring.

Treatment

Treatment of neurological movement disorders, particularly Parkinson's disease, focuses on relieving symptoms, improving daily functioning, and enhancing quality of life. Since there is currently no cure, management involves a combination of pharmacological treatments and supportive therapies. Medications such as Levodopa and Amantadine play a central role in controlling motor symptoms, while non-pharmacological approaches like physiotherapy, speech therapy, and counseling address physical, communication, and psychological challenges associated with the condition.

Levodopa [25] is the most effective and commonly prescribed medication for managing motor symptoms. It works by converting into dopamine once it reaches the brain, thereby compensating for the loss of dopamine-producing neurons.

Because dopamine itself cannot cross the blood-brain barrier, Levodopa is typically administered with carbidopa or similar agents to prevent its breakdown before reaching the brain and to reduce side effects such as nausea. Levodopa significantly improves symptoms such as bradykinesia, rigidity, and tremors, allowing patients to regain better control of movement. However, long-term use may lead to motor fluctuations and involuntary movements, requiring careful dose adjustment.

Amantadine [26] is another medication used in treatment, particularly in the early stages or as an adjunct to Levodopa therapy. It is believed to increase dopamine release and reduce its reuptake, while also influencing other neurotransmitter systems. Amantadine is especially helpful in reducing tremors and controlling dyskinesias associated with prolonged Levodopa use. Although generally well tolerated, it may cause side effects such as confusion or swelling in some patients, emphasizing the need for individualized treatment plans.

Supportive therapies are an essential component of comprehensive care. Physiotherapy helps maintain mobility, muscle strength, balance, and flexibility. Through targeted exercises and movement strategies, patients can improve posture, reduce stiffness, and lower the risk of falls. Regular physiotherapy also encourages physical activity, which has been shown to slow functional decline and enhance overall well-being.

Speech therapy addresses communication and swallowing difficulties that may arise as the disease progresses. Therapists work with patients to improve voice volume, articulation, and breathing control, helping them communicate more effectively. Speech therapy can also reduce the risk of aspiration and improve safety during eating and drinking. Counselling and psychological support play a crucial role in managing the emotional and mental health aspects of the disease. Depression, anxiety, and stress are common and can significantly impact quality of life. Counselling provides coping strategies, emotional support, and education for both patients and caregivers.

Conclusion

Parkinson's disease is a complex, chronic neurological disorder that affects both movement and overall quality of life. Its development is closely linked to the loss of dopamine-producing neurons, leading to characteristic motor symptoms such as tremors, rigidity, and slowed movements, as well as a range of non-motor challenges. Accurate diagnosis requires a careful combination of clinical evaluation and advanced diagnostic tools, while effective management depends on a multidisciplinary treatment approach. Although there is no cure, medications like Levodopa and Amantadine, along with supportive therapies such as physiotherapy, speech therapy, and counseling, play a vital role in controlling symptoms and

maintaining independence. Ongoing research and comprehensive care continue to offer hope for improved outcomes and better quality of life for individuals living with Parkinson's disease.

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