INTERNATIONAL MULTI DISCIPLINARY JOURNAL FOR RESEARCH & DEVELOPMENT
eISSN 2394-6334 Impact factor: 8.854 Volume 13, issue 05 (2026)

PARKINSON'S DISEASE: MULTISYSTEM APPROACH, PATHOGENESIS, AND MODERN TREATMENT STRATEGIES

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https://doi.org/10.5281/zenodo.20391818

Abstract. Parkinson's disease has undergone significant conceptual changes in recent decades. This pathology, previously considered primarily as a dopamine deficiency disease with motor disorders, is now interpreted as a complex multisystem disease that develops as a result of the interaction of genetic predisposition, environmental factors, and aging processes. In addition to dopamine deficiency, α-synuclein aggregation, mitochondrial dysfunction, oxidative stress, and neuroinflammation play an important role in the pathogenesis of the disease. Recent scientific evidence indicates that Parkinson's disease may not be limited to the central nervous system but may progress through the gut-brain axis. In particular, intestinal microbiota imbalance, impaired intestinal wall patency, and the spread of pathological proteins through the blood-brain barrier are important in the early stages of the disease. At the same time, non-anomotor symptoms observed in the prodromal period expand the possibilities for early detection of the disease. Clinically, Parkinson's disease manifests as motor (tremor, rigidity, bradykinesia, postural instability) and non-motor (pain, depression, cognitive impairment, sleep and autonomic dysfunction) symptoms. Diagnosis is primarily based on clinical assessment, and the current lack of standard biomarkers complicates early diagnosis. In treatment, levodopa is still the most effective agent, and it is often used in combination with dopamine agonists, MAO-B inhibitors, and other drugs. In advanced stages of the disease, instrumental and surgical methods such as deep brain stimulation and focused ultrasound yield effective results. Recent advancements include molecular profiling, neuroimaging, and artificial intelligence-based analysis methods, which contribute to a deeper understanding of Parkinson's disease as a multifactorial systemic disease. Current research focuses on an individualized approach (precision medicine), biomarker identification, and the development of disease-modifying therapies. Physical activity is also an important component in disease management, allowing for the reduction of symptoms, the maintenance of neuroplasticity, and the slowing down of disease progression. In conclusion, Parkinson's disease is a complex and multifactorial disease, and its effective management requires a multidisciplinary, biomarker-based, and patient-centered approach.

Keywords. Parkinson's disease, dopamine, α-synuclein, neurodegeneration, gut-brain axis, biomarkers, physical activity, deep brain stimulation

Introduction. Parkinson's disease is a progressive neurodegenerative disease of the central nervous system characterized primarily by the impairment of motor functions. In recent decades,

this disease has been recognized as a serious problem in the global healthcare system, as its prevalence rate is rising and the number of patients is increasing every year. The primary pathophysiological mechanism of the disease is associated with the gradual disappearance of dopaminergic neurons in the substantia nigra, a process that leads to dopamine deficiency. As a result, the activity of the basal ganglia is disrupted, and serious changes occur in the motor control system. The primary symptoms of Parkinson's disease (PD), a neurodegenerative condition, include bradykinesia, tremor, and rigidity. The progressive loss of dopaminergic neurons in the substantia nigra pars compacta (SNc) and the aggregation of α-synuclein (α-syn) into Lewy bodies (LBs), which progressively disseminate to various areas of the central nervous system and peripheral tissues, are two of its neuropathological hallmarks [1-4]. Genetic predisposition, aging, environmental exposures, and lifestyle factors interact in a complicated way to cause Parkinson's disease (PD). Core pathogenic processes, including as α-syn aggregation, oxidative stress (OS), mitochondrial dysfunction, and neuroinflammation, work in concert to drive disease development. The importance of peripheral-central communication channels in the onset and spread of disease has received a lot of attention lately. Pharmacotherapy continues to be the cornerstone for enhancing PD patients' quality of life. The restoration of dopamine that has been depleted in the brain is the main goal of the most widely utilized therapeutic medications. Nevertheless, these drugs do not halt the course of the illness; they simply relieve symptoms. This intrinsic drawback highlights the pressing need for more potent therapeutic approaches. With a focus on a comprehensive approach from etiology to therapy, this review attempts to methodically describe the network of Parkinson's disease pathogenesis and the development of its therapeutic approaches [5-10]. The most recent developments in α-syn-targeted immunotherapies, iPSC-based regenerative therapies, and gene therapies are included, along with a thorough study of possible candidate medications for Parkinson's disease and a critical evaluation of current drug therapy bottlenecks. Building on this basis, we further contend that in order to overcome current efficacy barriers, integrated, multi-target, and individualized therapeutic approaches are necessary for the future of Parkinson's disease care. While Parkinson's disease was previously considered to be associated only with motor symptoms such as tremor, rigidity, bradykinesia, and postural instability, modern scientific approaches now view it as a multisystem neurodegenerative disease. According to this approach, the disease is not limited to the brain but can also affect the peripheral nervous system, the autonomic system, and even the gastrointestinal tract. Recent studies indicate that the intestinal-cerebral axis plays a crucial role in the onset of Parkinson's disease. Disruption of the intestinal microbiota, inflammatory processes, and the spread of pathological proteins (α-synuclein) through the nervous system to the central nervous system are forming new theoretical directions for the development of the disease [11,12,13]. Furthermore, non-anomotor signs (sleep disorders, depression, cognitive changes, and autonomic dysfunction) that precede motor symptoms in the early stages of the disease are of diagnostic importance, expanding the possibilities for early detection. The global increase in Parkinson's disease, its complex pathogenesis, and the limited availability of effective treatment methods make this topic one of the most pressing scientific problems. Therefore, an in-depth study of disease mechanisms, the discovery of new biomarkers, and the development of innovative treatment strategies are among the primary directions of modern neurology. Significant progress has been made in PD research in recent years. At the molecular level, research has gone beyond conventional basic pathways including OS, mitochondrial failure, and neuroinflammation to include intricate networks involving connections across several organ systems, such as the gut-brain and spleen-brain axes. This has led to new theories that imply α-syn may go through neuronal pathways from the periphery to the central nervous system. On the therapeutic front, disease-modifying treatments

that target particular molecules like α-syn and c-Abl, as well as innovative techniques like immunotherapy, stem cell therapy, and gene therapy, have demonstrated significant promise in addition to novel drug delivery methods like levodopa inhalation powder and continuous subcutaneous infusions. In light of this, this review attempts to present a thorough and in-depth summary of the pathophysiology and therapeutic approaches for Parkinson's disease (PD), with the goal of providing insights for future research into PD mechanisms and the development of treatments and interventions [14,15,16].

The main purpose of the presented manuscript is to provide Parkinson's disease: multisystem approach, pathogenesis, and modern treatment strategies, based on the results of authoritative scientific works, regarding the relevance of improving their prevention and treatment.

Etiology and pathogenesis. Parkinson's disease has a multifactorial etiology, and its development is caused by the interaction of genetic, environmental, and neurobiological factors. The primary pathogenetic sign of the disease is the progressive loss of dopaminergic neurons in the substantia nigra of the midbrain. As a result of this process, dopamine synthesis decreases, and the motor control system through the basal ganglia is disrupted. Uncertainty surrounds the genesis of Parkinson's disease (PD), which may be influenced by genetics, environment, gender, age, and lifestyle. The incidence of Parkinson's disease (PD) gradually rises with age, and the biggest risk factor for the condition is aging. Males are more likely than females to have Parkinson's disease. Furthermore, research has shown that the gut flora is crucial in controlling motor dysfunction. Gastrointestinal problems are common in Parkinson's disease (PD) patients, and metabolites generated by the gut bacteria may affect brain neurons. Changes in the gut microbiota could therefore be a risk factor for Parkinson's disease (PD) [5-9].

The following main mechanisms are involved in the pathogenesis of the disease:

1.1. α-synuclein pathology

α-synuclein protein is misassembled to form Lewy bodies. This disrupts the neuron's internal transport system and accelerates cell death.

1.2. Mitochondrial dysfunction

Reduced energy production (deficiency of ATP) increases the sensitivity of neurons to oxidative stress.

1.3. Oxidative stress

Increased reactive oxygen species (ROS) lead to lipid peroxidation and DNA damage.

1.4. Neuroinflammation

The activation of microglial cells triggers a chronic inflammatory process.

1.5. Intestinal-cerebral axis theory

According to recent studies, the onset of the disease may occur in the peripheral system, specifically in the intestines. Impaired intestinal microbiota, increased intestinal permeability, and the spread of pathological proteins to the brain via the vagus nerve play an important role in the early stages of the disease [1-7].

2. . Clinical presentation

Clinically, the disease is characterized by two main groups of symptoms: motor and non-motor. The disease usually begins in the prodromal stage and progresses gradually.

2.1. Motor symptoms

• Tremor (often in the form of bloating)
• Rigidity (increased muscle tone)
• Bradykinesia (motor deceleration)
• Postural instability (imbalance)

Motor symptoms are associated with impaired basal ganglia-thalamus-cortex circulation.

2.2. Non-motor symptoms

• Pain syndrome (muscular and neuropathic)
• Depression and anxiety
• Cognitive impairments
• REM sleep disorder
• Vegetative dysfunction (blood pressure, digestive system disorders)

Non-manomotor symptoms often precede motor symptoms and may be of diagnostic importance [7-14].

3. Diagnosis and biomarker problem

Currently, there is no specific laboratory test for the diagnosis of Parkinson's disease; the diagnosis is primarily based on clinical criteria.

3.1. Clinical Diagnostics

• Neurological examination
• Presence of bradykinesia
• Tremor and rigidity assessment

3.2. Instrumental Methods

• MRI (assessment of structural changes)
• PET/SPECT (dopamine system activity)

3.3. Biomarker problem

The biggest problem is the lack of reliable biomarkers. Although α-synuclein, neurofilaments, and other proteins are promising, they have not yet become a clinical standard.

3.4. Artificial Intelligence and Modern Diagnostics

In recent years, AI-based models have been used to detect diseases at an early stage [3-11].

4. Treatment strategies

4.1. Pharmacological treatment

The main drug is levodopa, which is converted to dopamine and reduces symptoms. In addition:

• Dopamine agonists
• MAO-B inhibitors
• COMT inhibitors

Long-term levodopa:

• dyskinesia
• "wearing-off" phenomenon;

can cause issues like .

4.2. Surgical methods

• Deep brain stimulation (DBS)
• Focused ultrasound

These techniques significantly reduce movement symptoms.

4.3. Rehabilitation and an integrated approach

• Physiotherapy
• Speech therapy
• Psychological support
• Dietary and lifestyle changes [10-16].

5. Physical activity and neuroplasticity

Exercise is a very important therapeutic component in Parkinson's disease.

5.1. Exercise Effects

• Increases neuroplasticity
• Supports dopamine signaling
• Improves motor functions
• Reduces inflammation

5.2. Types of exercises

• Aerobic exercises (walking, running)
• Strength training
• Balance exercises

• Yoga and dance therapy

5.3. Preventive significance

Numerous epidemiological studies have shown that high physical activity can reduce the risk of developing Parkinson's disease [5-12].

6. Modern scientific directions

Current research focuses on the following areas:

• Precision medicine (individual treatment)
• Gene therapy
• Stem cell therapy
• AI-powered diagnostics
• Disease-modifying therapy [1-7].

Discussion.

Parkinson's disease is considered a complex, multifactorial, and progressive multisystem disease in modern medicine. Recent scientific research indicates the need to interpret this disease not merely as a simple motor disorder associated with dopamine deficiency, but as a complex pathological condition resulting from the interaction of genetic, environmental, and aging processes. In particular, the discovery of mechanisms such as the intestinal-cerebral axis, microbiota changes, and α-synuclein aggregation has fundamentally changed views on the pathogenesis of the disease. The clinical presentation of the disease is not limited to motor symptoms but also encompasses a wide range of non-anomotor signs. Underestimating these symptoms, particularly pain, depression, sleep disturbances, and cognitive decline, further worsens the quality of life for patients. Therefore, a comprehensive clinical approach is of great importance in assessing Parkinson's disease [2-8]. There are still problems in the diagnostic process, and the lack of clear and reliable biomarkers limits the early detection of the disease. Nevertheless, modern neuroimaging, molecular biology, and artificial intelligence-based technologies open up great prospects in this direction. In the future, it is expected that diagnostic systems based on biomarkers will allow for the detection of the disease at the prodromal stage. Regarding treatment, drugs that compensate for dopamine deficiency, especially levodopa, currently remain the primary therapeutic agent. However, the problem of decreasing the effectiveness of these drugs and the development of side effects during long-term use persists. Therefore, deep brain stimulation and other innovative technologies are of great importance in the severe stages of the disease. At the same time, physical activity and rehabilitation measures are becoming an integral component of managing Parkinson's disease. Regular exercise stimulates neuroplasticity, improves motor functions, and helps slow the progression of the disease. This makes it possible to consider physical activity not only as a means of treatment but also as a means of prevention [9-15].

Conclusion. Parkinson's disease is not limited to dopamine deficiency; it is a complex neurodegenerative process that encompasses all body systems. A complete understanding of its developmental mechanisms requires an approach at the molecular, cellular, and systemic levels.

Overall, effective management of Parkinson's disease requires a multidisciplinary approach, combining neurological, psychological, and rehabilitative care. Future research should focus on developing disease-modifying therapies, implementing individualized (precision medicine) approaches, and improving diagnostics and treatment using artificial intelligence.

Thus, early diagnosis, effective treatment strategies, and the promotion of a healthy lifestyle remain crucial for reducing the global burden of Parkinson's disease.

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