

Review Article

# Advances in Gait Disorders in Parkinson's Disease

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## Abstract

Parkinson's disease (PD) is a prevalent neurodegenerative disorder among the elderly, marked by progressive loss of dopaminergic neurons in the substantia nigra and the presence of Lewy bodies. The depletion of dopamine in the striatum and the resulting imbalance between dopamine and acetylcholine neurotransmitters lead to a gradual worsening of symptoms. These encompass both motor manifestations such as tremors, muscle rigidity, bradykinesia, and postural instability, as well as non-motor symptoms including sleep disorders, olfactory impairment, autonomic dysfunction, and cognitive or psychiatric disturbances. This review examines the pathogenesis, clinical progression, and therapeutic interventions for PD-related gait disturbances. The discussion focuses on potential mechanisms driving gait dysfunction, the evolution of symptoms across different disease stages, and current treatment options ranging from pharmacological to rehabilitative approaches. By integrating these perspectives, the article seeks to contribute novel insights into the diagnosis and management of PD, with the ultimate goal of improving patients' functional mobility and overall quality of life. Through a comprehensive analysis of existing evidence and emerging strategies, it highlights opportunities to address unmet needs in PD care, emphasizing personalized and multidisciplinary solutions to optimize long-term outcomes for affected individuals.

## Keywords

Parkinson's Disease, Gait Disorder, Pathogenesis, Clinical Manifestations, Treatment

## 1. Introduction

Parkinson's disease (PD) is a common age-related neurodegenerative disease in the elderly, characterized by progressive degeneration of dopaminergic neurons in the substantia nigra and the formation of Lewy bodies. As the dopamine neurotransmitter in the striatum area decreases and the balance between dopamine and acetylcholine neurotransmitters is disrupted, patients' clinical symptoms increase, mainly including tremor, muscle rigidity, slow movement, postural balance disorder, etc. as motor symptoms, as well as sleep

disorders, olfactory dysfunction, autonomic dysfunction, cognitive and psychological disorders as non-motor symptoms. Some scholars predict that by 2050, there will be 25.2 million Parkinson's disease patients worldwide, an increase of 112% from 2021. The prevalence of Parkinson's disease in 2050 will be 267 cases per 100,000 people, a substantial increase of 76% from 2021, while the age-standardized prevalence rate will be 216 cases per 100,000 people, an increase of 55% from 2021. From 2021 to 2050, the  $\geq$  age group of 80

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years saw the largest increase in the number of Parkinson's disease cases at 196% [1]. Gait disorder is one of the key motor symptoms of Parkinson's disease, affecting the quality of life of patients, and in severe cases, it can lead to disability, posing significant challenges for patients and their families, caregivers, communities, and society. Therefore, the diagnosis of gait disorder in Parkinson's disease is of great significance, which can improve the quality of life of Parkinson's disease patients and improve the prognosis of the disease. This review discusses the possible pathogenesis, clinical manifestations, and treatment options for gait impairment in Parkinson's disease from three perspectives: possible pathogenesis, different clinical manifestations in different stages of the disease, and treatment options. The aim is to provide new insights into the diagnosis and treatment of Parkinson's disease and improve the patients' mobility and quality of life comprehensively.

## 2. Pathogenesis of Gait Disorders

The automation of gait control during locomotion is mediated by a downstream neural circuit from the brainstem to the spinal cord, which is essential for robust walking and locomotion in animals [2]. Under normal conditions, the brain networks involved in gait regulation include the motor cortex, basal ganglia (BG), thalamus, cerebellum, mesencephalic locomotor region and central pattern generators [3]. According to existing studies, the core pathological features of PD are degeneration and necrosis of dopamine neurons in the substantia nigra compacta and noradrenergic neurons in the nucleus accumbens. At the same time, protein aggregates, known as Lewy bodies (LB), appear in dopaminergic, cholinergic, noradrenergic, and  $\gamma$ -aminobutyric acid neurons in these brain regions [4, 5]. This protein misfolding and aggregation plays an important role in the degenerative death of dopaminergic neurons. When PD patients present with significant clinical motor symptoms, 50% to 70% of substantia nigra compacta dopaminergic neurons apoptosis [6]. Oligomeric  $\alpha$ -syn may cause dopaminergic neuron death mainly through mitochondrial dysfunction, oxidative stress, glial inflammatory response, autophagy-lysosome dysfunction, cerebral microvascular injury, and cerebral lymphoid dysfunction, etc. [7-11]. substantia nigra compacta dopaminergic neuronal apoptosis leads to striatal dopamine deficiency, which affects the basal ganglia (BG) circuit associated with motor selection and planning, leading to severe movement impairments such as tremor, bradykinesia (slowness), and difficulty initiating voluntary movements (frozen gait or delayed initiation of motor programmes) [12]. Medium-sized spiny neurons in the direct pathway and Medium-sized spiny neurons in the indirect pathway of the BG loop control motor facilitation and motor inhibition, respectively, and they work in concert to accomplish normal movement [13]. Striatal dopamine deficiency causes an imbalance between the direct and indirect Medium-sized spiny neurons, which in turn leads

to motor symptoms in PD [14]. Since genome-wide association studies, more than 100 genes have been identified as PD risk-associated loci involving molecular pathways such as autophagy and apoptosis, oxidative stress, inflammatory immunity, and mitochondria [4]. LRRK2 is the causative gene with the highest mutation rate in PD, and the inhibition of LRRK2 activity has been suggested as a therapeutic option with clinical translational potential [15]. The dominant and recessive genes are not the same in Parkinson's disease. It has been found that the six genes mediating autosomal dominant inheritance of PD are SNCA, LRRK2, VPS35, EIF4G1, DNAJC13, and CHCHD2 [16]; whereas Parkin, PINK1, and DJ-1 are associated with autosomal recessive inheritance of PD. The mechanism of interaction between these gene mutations and gait disorders in Parkinson's disease remains to be further investigated.

## 3. Clinical Manifestations of Gait Disorders

Gait disorders manifest differently at different stages of disease progression. According to H-Y staging, PD can be initially categorized into early, middle and late stages [17]. In the early stage of the disease, gait disorders are mainly characterized by reduced stride length, altered walking rhythm and altered frequency of upper limb arm swing, slowed turn-taking, and weakened dual-tasking. Stride length: early Parkinson's disease patients have a reduced stride length compared to the healthy population. Although patients with gait disorders in Parkinson's disease can adjust their gait speed on their own, they are unable to adjust their stride length correspondingly in the absence of a control [18]; Walking rhythm: some studies have shown that in the early stage of Parkinson's disease, patients can show subtle changes in walking rhythm, which become more and more obvious as the disease progresses [19]; Alteration of upper extremity swing: some studies have shown that when patients with Parkinson's disease develop gait disorders in the early stage, the frequency of upper extremity swing is altered. Gait disturbance: it has been shown that in early Parkinson's disease patients with gait disturbance, the amplitude of the upper limb swing is mildly reduced, and the asymmetry of the swing is increased on both sides; slowed turn rate: it has been shown that early Parkinson's disease patients' turn rate is reduced compared with healthy patients; altered dual-tasking: gait disturbance in Parkinson's disease is usually associated with impaired dual-tasking, and in patients with Parkinson's disease, the attention being affected will significantly interfere with the walking state [2]. Patients with intermediate-term PD can have symptoms in both limbs and their movements become more sluggish. In a normal person, the process of a unilateral foot hitting the ground to that side's heel hitting the ground again while walking is known as a gait cycle. Depending on the position of the unilateral lower limb during walking, the normal human gait cycle can be divided into two

phases: the support phase and the swing phase. The support phase occupies 60% of the gait cycle, when the unilateral leg and foot bear most or all of the weight; the swing phase occupies 40% of the gait cycle, when the foot is not touching the ground and the weight is supported by the other leg and foot. The phase in which both feet are in contact with the ground at the same time for about 25% of a complete gait cycle is known as the double support phase; and the phase in which the unilateral lower limb supports the ground is known as the single support phase [20]. Patients with PD in the middle stage experience a marked increase in the bilateral lower extremity support phase, as well as a further decrease in the amplitude of the arm swing. This is accompanied by abnormal changes in posture, such as a forward body posture. Interference with gait kinematics can lead to further exacerbation of gait abnormalities, with freezing of gait (FOG) and panic gait, which is characterized by transient, episodic absence or marked reduction of stride movement despite the desire to move forward, and is often described by the patient as a difficulty in initiating the movement as if the feet were glued to the ground. Panic gait is more typical and is characterized by a forward leaning of the trunk during walking, small steps, rubbing of the feet on the ground, difficulty in starting and stopping, and a decrease in synergistic swinging of both upper limbs. In the advanced stages, gait disturbances worsen and motor dysfunctions (e.g., FOG) become frequent, accompanied by a decrease in balance and postural control, with a serious risk of falling, mobility with the help of assistive devices (e.g., wheelchairs), and even the inability to independently fulfill the needs of daily life [21].

## 4. Treatment of Gait Disorders

Pharmacologic therapy is still the preferred treatment for early Parkinson's disease. They mainly include levodopa (LD) or compound levodopa (compound LD), monoamine oxidase type B inhibitor (MAO-BI), dopamine agonists (DA), amantadine, and anticholinergic drugs. Anti-Parkinson's disease drugs. There are options for monotherapy or combinations of drugs. For example, apoptosis of dopaminergic neurons in the substantia nigra compacta leads to striatal dopamine deficiency, which in turn causes movement disorders such as gait abnormalities, and these symptoms can be relieved by oral levodopa [10, 22]. However, with the passage of time and disease progression, patients with PD may consider co-administration of drugs in addition to higher doses of levodopa therapy to increase efficacy. In the later stages of the disease, non-pharmacologic treatments can be considered when the combination of drugs still does not achieve the desired effect. Currently, non-pharmacological treatments include deep brain stimulation, which is an effective complement to pharmacological treatments. The new perceptible deep brain stimulation will record intracerebral signals in real time, allowing for precise point-of-contact selection and optimal postoperative control. Focused ultrasound, which combines focused ultrasound and magnetic resonance imaging, uses high-intensity focused

ultrasound to noninvasively target brain structures [23]. Repetitive transcranial magnetic stimulation, rehabilitation training technology, brain-computer interface technology, stem cell therapy, etc. Deep brain stimulation is a method of implanting an electrical stimulator in the brain of PD patients to stimulate the basal nucleus of the brain under the effect of electric field to alleviate the symptoms of dyskinesia, while at the same time combining with medication to reduce the dosage and side effects. Deep brain stimulation is used to reduce the dosage and side effects of medication to achieve the purpose of long-term treatment, and is now widely used in the treatment of drug-refractory middle- and late-stage PD patients [24]. Repetitive transcranial magnetic stimulation technology has been widely used in the clinic to realize the treatment of neurological and psychiatric disorders, and it is a new method of neuromodulation therapy that is safe, simple, with few side effects and a wide range of indications. In recent years, more and more studies have applied it to the assistive and rehabilitative treatment of PD [25]. The current rehabilitation exercise training includes relaxation training, plyometric training, postural training, balance training, gait training, and movement strategies [26]. The exact efficacy of some other emerging treatments has yet to be further clinically verified.

## 5. Summary and Outlook

This review summarizes the possible pathogenesis of gait disorders in Parkinson's disease, the clinical manifestations at different periods, and the treatment means. The pathogenesis of gait disorders in Parkinson's disease is complex, and many aspects of the disease still need to be further studied. Clinical manifestations are varied and similar to other diseases, requiring keen observation and accurate judgment by clinicians for early detection and early diagnosis, so that patients can receive the best treatment at an early stage. In recent years, the diagnosis and treatment mode of Parkinson's disease has changed a lot, the research of new drugs and non-pharmacological treatments continue to appear, but basically they are symptomatic treatments, which can only improve the patient's symptoms, and can't cure the disease very well. Research on gait disorders in Parkinson's disease, although some progress has been made in deepening the understanding of the mechanisms and developing effective treatments, however, there are still many challenges and unresolved issues. Future research needs to further enhance the exploration of the mechanisms of gait disorders in Parkinson's disease to reveal its complexity and multifactorial effects. It should also focus on developing more effective therapeutic strategies and applying existing emerging technologies more widely in clinical care in an effort to improve patients' quality of life.

## Abbreviations

PD      Parkinson's Disease

BG Basal Ganglia  
FOG Freezing of Gait

## Conflicts of Interest

The authors declare no conflicts of interest.

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