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Exploring the Complexities of Parkinson's Disease

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Abstract

Parkinson's disease (PD) is a neurological disorder, primarily affecting older adults, marked by both motor and non-motor symptoms. This review explores PD as a multisystem disorder that influences the central, enteric, and autonomic nervous systems, along with the immune system and gastrointestinal tract. Key pathogenic features include the degeneration of dopamine-producing neurons in the substantia nigra and the formation of Lewy bodies containing misfolded α-synuclein proteins. The bradykinesia, tremors, stiffness, and abnormalities in gait are motor symptoms caused by the nigrostriatal dopaminergic pathway degeneration. Non-motor symptoms, including cognitive decline, neurobehavioral issues, sleep disturbances, and autonomic dysfunction, often precede motor symptoms, significantly affecting quality of life. The pathophysiology of Parkinson's disease (PD) includes genetic mutations, abnormal protein buildup, mitochondrial dysfunction, oxidative stress, and neuroinflammation. Diagnosis is primarily clinical, supported by neuroimaging and biochemical markers. Treatment focuses on symptom management through pharmacological therapies like levodopa, dopamine agonists, and monoamine oxidase inhibitors, along with non-pharmacological interventions such as exercise and speech therapy. Surgical techniques like Deep brain stimulation and newly developed gene therapies may be beneficial in advanced situations. This review highlights the necessity for ongoing research to better understand PD's underlying mechanisms and to develop more effective treatments to improve patient outcomes and quality of life.

Keywords: Parkinson's disease, substantia nigra, motor symptoms, Lewy bodies, surgical techniques, pharmacological therapies

INTRODUCTION

Parkinson's disease (PD) is an idiopathic nervous system illness that can cause symptoms in the motor and non-motor systems. It is a long-term, progressive neurodegenerative illness that primarily affects the elderly but can sometimes strike people considerably younger individuals [1]. Parkinson's disease (PD) is currently referred to as a multisystem neurodegenerative disease since it concurrently affects the autonomic nervous system, enteric nervous system, central nervous system, adaptive immune system, and gastrointestinal (GI) tract. After Alzheimer's Disease, Parkinson's disease (PD) is the second-most common age-related neurodegenerative illness. 'Movement Disorder' is another name for PD. The dopamine-producing nerve cells degenerate in the substantia nigra region of the brain in this disease. Substantia Nigra is situated on each side of the mid-brain and is a part of basal ganglia, a region of the brain that is involved in controlling movement through the assemblies with the motor cortex. The motor symptoms of PD include bradykinesia, tremors, rigidity, gait disturbances, etc. resulting from the deterioration of the Nigrostriatal Dopaminergic pathway. Moreover, neurobehavioral problems (such as anxiety and depression), dementia, and autonomic dysfunction (such as orthostasis and hyperhidrosis) have been linked to Parkinson's disease (PD) [2]. Parkinson's disease often manifests non-motor symptoms before the development of conventional motor symptoms. Non-motor symptoms often include

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olfactory dysfunction, cognitive decline, mental problems, sleep disturbances, autonomic dysfunction, pain, and exhaustion. These signs are typical of early-stage Parkinson's disease and are linked to a lower quality of life in terms of one's health.

Parkinson's disease is characterized by Lewy bodies, which are collections of misfolded α-synuclein proteins. However, Lewy bodies are not exclusive to Parkinson's disease and can also be found in several other neurodegenerative conditions, making Parkinson's disease a spectrum disease with many different clinical subtypes. The actual aetiology of PD is still mostly unknown. Only a portion of the true aetiology of Parkinson's disease has been determined. It has been investigated that the progression of PD is influenced by several factors such as aging, heredity, and environmental factors. Over the years, research has shown that people experience Parkinson's disease in different ways, and corresponding variations in clinical and epidemiological features have been documented in each gender. PD is twice as common in males as in women [3].

PATHOPHYSIOLOGY OF PD

Parkinson's disease (PD) is defined pathologically by the development of Lewy bodies, a pathological hallmark, in Dopaminergic neurons and loss or degeneration of dopaminergic (Dopamine-producing) neurons in the substantia nigra. Pathologic alterations may occur two decades, or longer before overt symptoms appear. There is a noticeable reduction in motor control because of this selective loss of dopamine-generating neurons. Alpha-synuclein and ubiquitin are two of the presynaptic proteins found in Lewy Bodies, or aberrant intracellular aggregates, which can negatively impact normal neuron function [4]. When α-synucleinopathy is found and substantia nigra degradation takes place, typical motor symptoms of Parkinson's disease (PD) become noticeable. Dopaminergic cells loss in the substantia nigra is the primary cause for the development of PD. However new research indicates that LC norepinephrine is a crucial part of this illness. The peri-LC sub coeruleus area and the nucleus as a whole experience LC cell loss in Parkinson's disease (PD). The surviving neurons have changed phenotypes and show substantial shrinking [5].

Neuronal death is influenced by genetic mutations that code for central nervous system proteins. Alpha-synuclein exhibits aberrant behavior and self-aggregation. This insoluble, aggregated alpha-synuclein is a primary component of Lewy Bodies, the cellular inclusions that characterize Parkinson's disease. Furthermore, pathways intended to degrade aberrant proteins, such as the ubiquitin-proteasome system, are also compromised. Other compromised mechanisms that might contribute to Parkinson's disease (PD) include mitochondrial malfunction or aberrant oxidative stress resulting from reactive oxygen species that cause neuronal damage [6].

One of the main pathogenic features of PD is the loss of dopaminergic neurons inside the Substantia nigra pars compacta (SNpc). The SNpc's most severely affected region is usually the neurons of the ventrolateral tier, which project to the striatal dorsal putamen. Another aspect of the pathophysiology of Parkinson's disease is neuroinflammation. Parkinson's disease is known to be associated with an active inflammatory response in the brain, which is mostly mediated by local astrocytes and microglia. This fact has been mostly ignored, though. In regions of Parkinson's disease neurodegeneration, reactive gliosis, which is caused by activated astrocytes, and microgliosis, which is caused by microglial activation, both take place. Microglia and astrocytes are both engaged in removing extracellular debris, which may help neurons survive. Pro-inflammatory cytokines, hazardous reactive oxygen and nitrogen species, and trophic substances like brain-derived neurotrophic factor and glial-derived neurotrophic factor can all be released by activated microglia. It is still unknown how these effects balance out in terms of being advantageous or detrimental to neurons [7].

Parkinson's disease pathogenesis seems to be caused by a complicated interaction between abnormal α-synuclein aggregation, mitochondrial malfunction, problems with lysosomes or vesicle trafficking, synaptic transport problems, and neuroinflammation. All of these disease processes lead to increased

death of neurons, mostly dopaminergic neurons, but several other motor and non-motor circuits are also affected by the neuropathology [6].

CLINICAL PRESENTATION

Four main components are combined in the clinical presentation of Parkinson's disease (PD): motor symptoms, cognitive abnormalities, behavioral/neuropsychiatric abnormalities, and autonomic nervous system dysfunction symptoms [7].

Motor Symptoms

Four motor cardinal symptoms of Parkinson's disease (PD) can be grouped together under the acronym TRAP: rigidity, postural instability, akinesia (or bradykinesia), and tremor at rest. Furthermore, flexed posture and freezing (motor blocks) have been recognised as characteristic features of Parkinsonian diseases, with Parkinson's disease (PD) being the most common kind [8]. Studies on pathology and neuroimaging indicate that motor symptoms of Parkinson's disease (PD) do not appear until 50–70% of substantia nigra neurons have deteriorated [9].

Parkinson's disease (PD) is mostly associated with bradykinesia, or slowness of movement, however it can also be seen in other disorders, such as depression. One of the main characteristics of illnesses affecting the basal ganglia is bradykinesia, which includes problems with organizing, starting, and maintaining movement as well as carrying out sequential and simultaneous activities [10].

The most prevalent and most identifiable PD symptom is resting tremor. The distal part of an extremity is where unilateral tremors are most evident, and they often occur at a frequency of 4-6 Hz. Supination–pronation tremors, often known as "pill-rolling" tremors, are defined as tremors that propagate from one hand to the other. Many PD patients also exhibit postural tremors, which are more noticeable and incapacitating than rest tremors and may be the initial sign of the illness [11].

Increased resistance and the "cogwheel" phenomena are characteristics of rigidity. These are often present during all phases of passive limb movement (flexion, extension, or rotation about a joint), and they are particularly noticeable in conjunction with underlying tremor. It can happen both close to the body (hips, shoulders, neck) and far from it (wrists, ankles) [12]. Patients with Parkinson's disease (PD) are prone to have postural instability later in the illness course, which increases their risk of falling [13]. Rigidity is frequently linked to postural abnormalities that cause flexed elbows and knees, as well as flexed neck and trunk posture. Freezing, sometimes referred to as motor blocks, is one of the most debilitating signs of Parkinson's disease (PD). One type of akinesia, or immobility, is freezing. Although it is a defining feature of Parkinson's disease, freezing is not always evident [13].

In addition to the 'classic' motor symptoms already stated, there are other motor manifestations observed. Kyphosis, scolosis, stooped posture, shaky gait, masked facial expression (hypomimia), decreased rate of eye blink, blurred vision, altered upward gaze, dystonia, and speech related problems, such as palilalia (word or phrase repetition) or hypophonia (increasingly soft voice), are a few of these [1].

Non-Motor Manifestations

Alterations in cognition, behavioural and neuropsychiatric disturbances, autonomic nervous system failure, sensory abnormalities, and sleep difficulties are among the non-motor symptoms of Parkinson's disease (PD). Remarkably, a prodrome of non-motor symptoms may appear years before motor signs of Parkinson's disease. These include erectile dysfunction, depression, orthostatic hypotension, REM sleep disruption, hyposmia (altered perception of smell), urge urine incontinence, and constipation [1].

Almost every facet of autonomic function may be impacted by autonomic dysfunction, which is prevalent in Parkinson's disease. These autonomic dysfunctions include constipation, orthostatic hypotension, and problems with the urine and sex [14, 15]. Sensations of pain that have been

characterized as scorching, tingling, or lancinating might be localized or widespread. Pain is thought to afflict almost two-thirds of people with Parkinson's disease (PD). Dystonia and illness-related joint and skeletal abnormalities are widespread in PD [1]. According to a recent poll, 76% PD patients out of 100 people with Parkinson's disease, reported having distress or discomfort. Parkinson's disease pain has been grouped into five different categories and these are: akathitic discomfort, primary or central Parkinsonian pain, dystonia-related pain, radicular or neuropathic pain, and musculoskeletal pain [14].

There are issues with memory recall, decision-making, multitasking, and visuospatial perception. PD dementia develops later in the illness. Parkinsonian syndrome, or DLB, is linked to early-onset dementia. Parkinson's disease is linked to a six-fold greater risk of dementia development. Dementia is more common in Parkinson's disease (PD) patients with a considerable family history of the illness. PD patients may have hallucinations and psychosis. The most prevalent psychotic symptom is visual hallucinations. Parkinson's disease sufferers have mood disturbances such as apathy, anxiety, and sadness. Mood disorders are one of the most troublesome non-motor complications in PD patients whether early or late in the disease. Regarding PD, anxiety is the most common mental mood condition, affecting around one-third of patients. It is also possible to have abulia, or the inability to think or act, and apathy, or loss of drive [1].

In the context of Parkinson's disease (PD), disturbed or poor sleep is quite prevalent and may approach 90%. With many nocturnal awakenings, sleep fragmentation is the most prevalent kind of insomnia in people with Parkinson's disease. Recently, there has been a lot of attention focused on REM sleep behavior disorder (RBD), which is characterized by the capacity to move during REM sleep. RBD is a risk factor for developing PD as well as a symptom of PD [14]. Patients with Parkinson's disease (PD) may have irregular sleep patterns due to a 50% loss of hypocretin (orexin) neurons [13].

Roughly 90% of PD patients appear to have defective scent detection and discrimination, a sensory impairment [15]. Most PD patients who are impacted are often ignorant of the deficiency. Olfactory testing aids in the differentiation of idiopathic Parkinson's disease (PD) from other Parkinsonian syndromes [1].

RISK FACTORS ASSOCIATED WITH PD

Environmental and genetic variables have a role in the aetiology of Parkinson's disease (PD) [8]. The biggest risk factor for Parkinson's disease is advancing age, but genetics and environment have an impact on the illness's likelihood and progression [6]. According to recent studies, aging and environmental stress both may encourage neuropathology. Persistent low-level inflammation in the brain is promoted by aging-related stress or exposure to environmental contaminants (such as pesticides, drugs of abuse, etc.) In brain neurons, this inflammatory process eventually results in cellular senescence [1].

There have been several other risk variables proposed, but the epidemiologic data is not as strong. These include living in rural areas, working in agriculture or farming, consuming milk, consuming well water, being overweight, being exposed to hydrocarbon solvents, living in urban or industrialized areas and being exposed to Lead, Manganese, and Copper, eating a high-iron diet, having a history of anemia, and having more education [1]. Variability in the link between exposure and disease suggests that the phenotypic of disease is influenced by gene-environment, environment-environment, and other exposure dynamics [7].

It has also been proposed that welding and exposure to heavy metals including iron, manganese, copper, lead, amalgam, aluminium, or zinc enhance the risk of Parkinson's disease (PD) by causing metals to accumulate in the substantia nigra and increasing oxidative stress [9].

The higher risk of illness linked to a family history of Parkinson's disease or tremor suggests that heredity plays a role in Parkinson's disease [4]. Currently, the most emphasis has been focused on

mutations in the genes SNCA, LRRK2, PRKN, PINK1 and GBA. All SNCA mutations have some characteristics in common, such as an earlier age at which the disease manifests, a quicker progression of motor symptoms, and the existence of notable non-motor symptoms, such as a rapid deterioration in cognitive function. There is now strong evidence connecting seven distinct LRRK2 mutations to Parkinson's disease [10]. Since LRRK2 mutations cause 1% of sporadic Parkinson's disease worldwide and around 4% of familial Parkinson's disease, they are the most common cause of genetic Parkinson's disease. The most prevalent LRRK2 mutation causes an amino acid change at Gly2019Ser, which raises the protein's kinase activity [4].

Parkinson's disease autosomal recessive versions are linked to Parkin, PINK1, and DJ-1. Mutations in the parkin protein is one of the frequent causes for the development of autosomal recessive Parkinson's disease. Parkinson's disease mutations are observed in up to 50% of familial cases and around 15% of sporadic cases in people whose condition began before the age of 45. Less often, mutations in PINK1 and DJ-1 account for 1-8% and 1%, respectively, in early-onset sporadic Parkinson's disease [4].

There have been recent worries that COVID-19 may make people more susceptible to Parkinsonism, while there is now just anecdotal data to support this theory. Parkinson's disease and COVID-19 both, cause hypomania and after nasal entrance into the brain, SARS-CoV-2 may start a chain reaction of neurodegeneration. Close observation will determine whether the already rapidly increasing prevalence of Parkinson's disease picks up speed because of the global COVID-19 pandemic, similar to what happened after the 1918 influenza pandemic [10].

DIAGNOSIS

The diagnosis of Parkinson's disease cannot be made without the finding of unequivocal bradykinesia, although individuals with monosymptomatic rest tremors who have anomalies of striatal dopamine on functional imaging exist [11]. Bradykinesia along with stiffness and resting tremor are the hallmarks of Parkinsonian motor characteristics, which are used to make a clinical diagnosis of Parkinson's disease. Usually, postural instability is a sign of a more advanced illness. Lewy bodies in the remaining SNpc neurons and moderate-to-severe neuronal loss in the SNpc, together with the absence of pathological evidence for other disorders that cause parkinsonism, are often required for the diagnosis of Parkinson's disease [4].

PET or SPECT imaging can be used to assess pre-synaptic and post-synaptic striatal dopaminergic function utilizing a range of radioactive tracers [12]. To evaluate the reduction of SNpc dopaminergic nerve terminals that project to the striatum, two possible imaging markers that may be utilised are positron emission tomography (PET) and single photon emission computed tomography (SPECT). These imaging techniques can assist in differentiating Parkinson's disease with motor symptoms from conditions (such as essential tremor) that do not result in the death of SNPc neurons. Because dopamine imaging techniques cannot consistently differentiate Parkinson's disease from other parkinsonian disorders linked to nigral degeneration, such as atypical parkinsonism, they are insufficient in diagnosing Parkinson's disease on their own. The diagnosis of Parkinson's disease may be made using standard MRI, but cutting-edge methods like diffusion tensor imaging in conjunction with high- and ultra-high-field (7 Tesla) MRI are being investigated for early Parkinson's disease detection. The concentration of α-synuclein, DJ-1, tau, and β-amyloid as well as the activity of β-glucocerebrosidase in cerebrospinal fluid are being examined as possible biochemical biomarkers of early Parkinson's disease. Genetic testing can help in the diagnosis of Parkinson's disease in those whose family members have a recognized monogenic variant of the disease. However, as most monogenic causes of Parkinson's disease are only partially penetrated, a positive genetic test results in no conclusive diagnosis in an asymptomatic person [4].

TREATMENT

Since Parkinson's disease (PD) is progressive, symptoms progressively get worse. Although several medicines can help manage symptoms and improve quality of life, there is currently no known cure for

Parkinson's disease (PD). Based on the patient's specific symptoms, stage of sickness, and overall health, the best course of action is decided. Depending on the disease's stage, several treatment methods are available. Parkinson's disease treatments solely address the illness's symptoms [4].

The illness's fundamental causes are diverse, and Parkinson's disease neurodegeneration is caused by a variety of cellular mechanisms. The basis of therapy for motor symptoms continues to be medications that increase intracerebral dopamine concentrations or activate dopamine receptors These drugs include monoamine oxidase type B inhibitors, dopamine agonists, levodopa, and, less often, amantadine. Early in the course of the disease, dopaminergic medications are a reliable way to treat bradykinesia and stiffness. Inhibitors of monoamine oxidase type B are only somewhat helpful at best. More severe symptoms and gradual impairment require the use of dopamine agonists or levodopa. Tremor responds inconsistently to dopamine replacement treatment, especially at lower dosages, in contrast to bradykinesia and rigidity. Anticholinergic medications, including clozapine or trihexyphenidyl, can be useful in treating tremors. Levodopa and dopamine agonists can both cause oedema, nausea, and somnolence throughout the day, although dopamine agonists are more likely to cause these adverse effects. Dopamine agonists are often not given to older patients, especially those with cognitive impairment, as they are also more frequently linked to hallucinations. The greatest clinical relief is seen with levodopa; nevertheless, long-term treatment is linked to motor problems, including dyskinesia and motor fluctuations. A levodopa-sparing first treatment with a monoamine oxidase type B inhibitor or dopamine agonist may be explored to postpone the beginning of these problems.

Clozapine is the most effective treatment for psychosis in Parkinson's disease patients. However, because clozapine can trigger an unusual adverse medication response called agranulocytosis, which can be fatal, regular haematological status monitoring is required.

Cholinesterase inhibitors, such as rivastigmine, may lessen delusions and visual hallucinations in Parkinson's disease patients experiencing dementia. The most widely prescribed drugs for treating depression in Parkinson's disease patients are selective serotonin reuptake inhibitors, such as citalopram, escitalopram, fluoxetine, paroxetine, and sertraline; however, there is no proof to support the use of a particular selective serotonin reuptake inhibitor [4].

Surgical treatment for motor symptoms of PD includes Deep Brain Stimulation (DBS). When levodopa does not improve Parkinsonian motor characteristics, but motor fluctuations and dyskinesia become incapacitating, surgery may be necessary. Deep brain stimulation can improve certain non-motor characteristics, such as non-motor fluctuations, sleep-related symptoms, and behavioral abnormalities. However, more research is required to determine the contributions of the stimulation versus the effect of improved motor function and decreased use of dopaminergic medications that are used in conjunction with deep brain stimulation. According to the results of many clinical trials, deep brain stimulation of the globus pallidus internus or the subthalamic nucleus is beneficial for moderate-to-severe Parkinson's disease. About 10 to 13 years typically pass following a Parkinson's disease diagnosis before surgical therapy is initiated [4]. In DBS, an electrode that provides continuous high-frequency electrical stimulation is surgically inserted in the ventral intermediate nucleus, globus thalamus, or subthalamic nucleus (STN) DBS is reversible, does not destroy brain tissue, and may be modified to account for the course of the disease [1].

One potentially helpful strategy to lessen the motor symptoms of progressive Parkinson's disease is gene therapy. Neither the neurodegenerative process nor non-motor symptoms are affected by the gene treatments that are currently being researched. Four phase I/II clinical investigations are being conducted on patients with Parkinson's disease (PD). The lentiviruses (LV) and adeno-associated viruses (AAV2, AAV5) are the most frequent vectors. The viruses seek to transduce therapeutic genes into striatal, nigral, or subthalamic nucleus cells via direct stereotactic injection to aid in the restoration

of normal function or to offer neuroprotection against additional degeneration. Using lentivirus, adenovirus, and adeno-associated virus-based vectors to stimulate glial cell line-derived neurotrophic factor (GDNF) is one method of disease modification. Utilizing transgenes to decrease the production of α-synuclein, which disrupts neural activity, is a further strategy. As parkin appears to be a neuro-protective substance, viral vectors also target it. Further potential gene therapy strategies include Complex 1, MicroRNA, and 4E-BP targets [1].

The foundation of PD therapy consists of medical interventions. Pharmacotherapy and non-pharmacological alternative methods include education, exercise, speech treatment, support groups, and diet are among them. Therapy strategies are based on the patient's age, illness stage, symptoms, and therapy benefit/risk ratios. Alternative therapies that don't include drugs include speech therapy, exercise, education, support groups, and diet. Physical treatment and regular exercise can significantly help with some of the physical symptoms of Parkinson's disease (PD), such as curved posture and joint stiffness. Exercises aimed at increasing strength, balance, and flexibility ought to be prioritized. Certain aspects of the illness may seem more manageable to the patient [1].

CONCLUSION

Parkinson's disease (PD) is a progressive neurodegenerative illness that largely results from the death of dopamine-producing neurones in the substantia nigra. It affects both motor and non-motor systems. Non-motor symptoms, such as cognitive decline and sleep difficulties, have a substantial influence on quality of life and frequently manifest earlier than motor symptoms, which include tremors and stiffness. The exact cause of PD remains unclear, involving a mix of genetic, environmental, and aging factors. Current treatments focus on symptom management, with medications like levodopa and dopamine agonists being the mainstay, though they come with side effects. Surgical options, such as deep brain stimulation, provide relief in advanced cases. New therapies like gene therapy are being explored too. Understanding PD's complex pathology, including protein aggregation and neuroinflammation, is vital for developing better treatments. Continued research is crucial for discovering more effective treatments and enhancing patient outcomes.

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