New Therapeutic Era for Parkinson's Disease

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Abstract

The progressive neurodegenerative condition known as Parkinson's disease is characterized by both motor and non-motor symptoms. The condition comprises of reduction in dopamine levels by targeting neurons that produce dopamine inside the substantia nigra, which primarily cause movement issues such as tremors, sluggish motions, muscular stiffness, and balance issues. The condition is made more difficult to manage by non-motor symptoms including depression, sleep disorders, and cognitive impairment. It is believed that both genetic and environmental factors play a role, while the precise explanation is still unclear. Common applications for the treatment of this disease include deep brain stimulation, Repetitive transcranial magnetic stimulation, and many forms of gene therapies, while these approaches do not completely cure Parkinson's they may help in alleviating symptoms and provide relief. In addition, for the restoration of motor functions and to improve the standard of life physical therapy and exercises are incorporated for a better quality of life and to improve efficiency of other treatments being applied. Due to the ambiguity of the definite cause of Parkinson's Disease, advances in technology are further being every day such as the incorporation of machine learning, robotics rehabilitation, and virtual reality in the present treatments to elevate patient outputs. Moreover, the improvement in patients' standard of life greatly affected caregivers, psychological support, and rehabilitation.

Keywords: Neurodegenerative, Parkinson's disease, Dopamine, Physical therapy, Rehabilitation

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Introduction

Parkinson's disease (PD) is a chronic and escalating neurodegenerative disorder that primarily affects movement control and usually occurs in older adults. The illness, which was first recognized and described by James Parkinson in 1817, developed gradually and gradually. A possible hereditary component exists; however, family instances are uncommon and usually happen infrequently (Lee et al., 2024). The hallmark of Parkinson's disease is the deliberate death of dopaminergic neurons in the Substantia Nigra, which lowers dopamine levels in the striatum and impairs motor function. Bradykinesia, muscular stiffness, resting tremors, and unstable posture are the main motor signs. Furthermore, a variety of non-motor symptoms, including sleep disorders, dementia, sensory problems, and autonomic dysfunctions, are frequently faced by people with Parkinson's disease (Chia et al., 2020). Parkinson's disease cannot yet be diagnosed. Nonetheless, a variety of symptoms and diagnostic procedures are combined. Scientists have looked at several biomarkers to detect Parkinson's disease early and slow down the progression of the illness (Wang et al., 2020). Environmental pollutants are the main cause of Parkinson's disease; some prominent offenders include air pollution, industrial solvents like trichloroethylene, and certain pesticides. These are especially connected via both epidemiologic and preclinical investigations, while additional toxicants may also be linked to Parkinson's disease. Numerous of these chemicals harm mitochondria, which have been found to be impaired in Parkinson's disease. Furthermore, people are exposed to these toxicants through a variety of routes, such as ingestion and inhalation (Dorsey et al., 2024).

Pathophysiology of Parkinson's Disease

The primary cause of Parkinsonism is malfunction in the basal ganglia, a network of linked brainstem and subcortical nuclei that are essential for regulating the commencement and duration of activities. Nigrostriatal insufficiency is specifically caused by the loss of dopaminergic neurons in the substantia nigra of the midbrain, which interferes with communication to the corpus striatum (Ye et al.,2023). Long before motor symptoms appear, neurodegeneration of the basal ganglia and the reduction in dopaminergic neurons in the substantia

nigra start. By the time motor symptoms appear, nearly half to two-thirds of nigral dopaminergic neurons have been lost, and as much as four-fifths of synaptic integrity has been diminished (Zhang et al., 2023). The existence of proteinaceous clumps in neurons known as Lewy bodies (LBs) and Lewy neurites is the second characteristic of Parkinson's disease. Both within and around the SNc, such particles have been seen. According to more updated research, LBs resemble caged wheel-like structures, with hydrophobic α-syn species lying closer to a core made primarily of lipids and negatively charged α-syn species forming the aggregate's outer layer (Vázquez et al., 2021).

The pathogenesis of Parkinson's disease is caused by a combination of inflammation of the brain, lysosomal and vesicle transport abnormalities, mitochondrial dysfunction, α-synuclein aggregation, and synaptic transport disorders (Figure 1). These elements simultaneously impact motor and non-motor pathways and hasten the death of dopaminergic neurons. Bradykinesia is caused by the imbalance along direct and indirect basal ganglia pathways, which is upset by the loss of nigrostriatal dopamine, which results in a reduction in dopamine in the corpus striatum (Bloem et al., 2021).

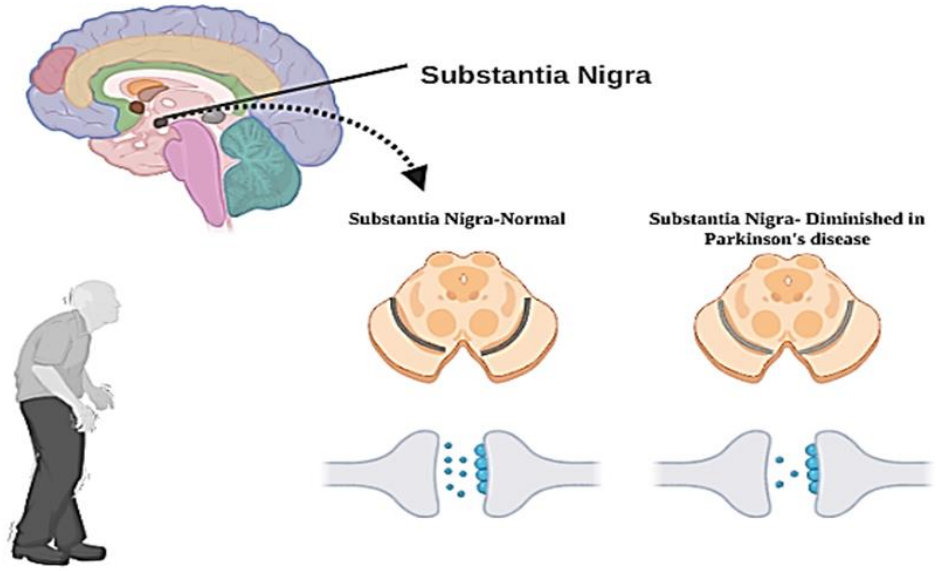

Fig. 1: Pathophysiology of Parkinson's disease (Retrieved from biorender)

Factors

About a small fraction of Parkinson's disease patients have a genetic component. Just a small percentage of those with Parkinson's disease have even common genetic variants, such as those in the LRRK2 gene, and only between a quarter and almost half show incomplete penetrance. In addition to hereditary factors, environmental variables are important in the occurrence of the illness. Genetics most certainly plays a role in Parkinson's disease by determining which individuals are more susceptible to the ailment than those who are exposed to contributory factors (Dorsey et al., 2024). Environment-related factors such as head traumas, rural life, pesticide exposure, depression and anxiety, and dairy intake have been associated with an elevated risk of Parkinson's disease. On the other hand, a decreased risk of Parkinson's disease has been linked to physical inactivity, smoking, drinking coffee or alcohol, and having higher blood uric acid levels (Lee et al.,2024).

Diagnostic Approaches: Early Detection and Precision Medicine

To diagnose Parkinson's disease, imaging studies and clinical examination are crucial. The ventrolateral substantia nigra pars compacta is where neuronal loss in the initial phase of Parkinson's disease first takes place. The posterior putamen next becomes concerned and eventually other striatal areas. During the early stages of Parkinson's disease, structural MRI has shown gradual brain shrinkage (Zhang et al., 2023). Using a variety of metrics, including language information, gait sequences, force tracking data, scent recognition, and random cardiovascular oscillations, many techniques have been put forth to help identify Parkinson's disease (PD). One method is to evaluate Parkinson's disease-related speech abnormalities captured on cell phones using the sawtooth-inspired pitch estimator technology (Wang et al., 2020). The majority of individuals with Parkinson's disease have vocal cord dysfunction beginning as early as stage 0 of the five phases of Parkinson's disease. Voice modulation is frequently associated with dysphonia and dysarthria. Running speech tests, which provide a realistic assessment of disability, or persistent phonation, which involves asking patients to preserve the pitch of a single vowel for as long as feasible, are two methods used to evaluate vocal dysfunction (Govindu et al., 2023). Genetic testing for Parkinson's disease is challenging since only a minority, approximately 5 to 10% of PD individuals have genetic variations. Mutations in genes including SNCA, LRRK2, and VPS35 are linked with the hereditary singular and idiopathic types of Parkinson's disease (Uwishema et al., 2022).

Pharmacological Interventions

The mainstay of the current therapy strategy for Parkinson's disease is levodopa or dopaminergic agonists, which alleviate motor symptoms by restoring neurotransmission and so targeting the illness's fundamental pathogenesis (Table 1). Wearing off sensations and other motor difficulties are among the worst adverse effects that might arise from long-term usage of these drugs. Levodopa-induced problems are managed with additional dopaminergic drugs, including monoamine oxidase type B inhibitors, dopamine receptor agonists, and the NMDA receptor antagonist amantadine, when there are variations in symptom management (Chia et al., 2020). Parkinson's disease is

initially treated with dopamine agonists as a first-line medication. These drugs were first developed as levodopa adjuncts to aid people with dyskinesias by lowering the dosage of levodopa needed by a reduction of about one-fifth to one-third (Schneider et al., 2020). The treatment of Parkinson's disease often involves the use of selegiline, a specific monoamine oxidase-B inhibitor. It increases the amount of dopamine in the brain by blocking the enzyme that breaks down dopamine (Gandolfi et al., 2024). For stiffness, tremors, and trouble, dopamine-based therapies, such as levodopa formulations and dopamine agonists, are believed to be successful. Notably, levodopa can increase the length of steps and gait speed, whereas dopamine agonists can enhance turning and gait beginning. It should be mentioned that medications for non-motor symptoms, such as anxiety, sadness, and cognitive decline, might enhance gait (Harsanyiova et al., 2020). The ability of anticholinergic drugs, such as Artane and Cogentin, to lessen tremors in individuals with Parkinson's disease has led to their approval. They function by reestablishing the proper ratio of dopamine to acetylcholine in the brain (Chopade et al., 2023). Although there is currently insufficient data and clinical studies to draw firm conclusions, disease-modifying transgenes have the potential to decrease the course of Parkinson's disease. The non-motor symptoms of the condition are not addressed by these treatments, which concentrate on reducing motor symptoms (Lee et al., 2021).

Table 1: Common Medications for Parkinson's Disease

Medication Class	Purpose/Benefit	References
Levodopa	Converts to dopamine in the brain and improves motor symptoms such as tremors, rigidity, and bradykinesia.	(Muleiro et al., 2024)
Dopamine Agonists	Often used in conjunction with levodopa or in the initial phases of Parkinson's disease to replicate the brain's dopamine mechanism.	(Currie et al., 2024)
Anticholinergics	Minimize muscular stiffness and tremors by inhibiting acetylcholine.	receptors (Seppänen et al., 2024)
Monoamine Oxidase B Inhibitors	Increase dopamine activity by preventing dopamine from being broken down.	(Seppänen et al., 2024)

Gene Therapy and Cell-Based Approaches

Restoring lost or injured neurons is the goal of stem cell treatment, whereas gene therapy focuses on repairing genetic defects or controlling gene expression to stop the course of illness. Furthermore, mitochondrial enhancers reduce degeneration and increase cellular energy production (Mahboob et al., 2024). Researchers have shown that gene therapy can lessen neurodegeneration in clinical trials of Parkinson's disease by encouraging amplification of regulators of mitochondrial oxidative stress and circumstances, including PGC-1α, HSP70, and TFEB. This treatment may be beneficial for the degeneration of brain disorders (Chen et al., 2020). Biologic therapies such as Affitope PD01A and UB-312 prevent the further production of Lewy bodies by preventing the disintegration of dopaminergic neurons. This and many other anti-inflammatory drugs are further being studied and researched to further surpass the progression of the disease causing the overall neuron reduction. The use of anti-aggregation is the habitual mode of preventing the synthesis of Lewy bodies which then hinder their neurodegeneration (Chopade et al., 2023). Since dopamine is unable to pass the blood-brain barrier, the replacement treatment for dopamine relies on L-DOPA. Upon entering the brain, it is then reformed into dopamine by the remaining nigrostriatal neurons with the help of other neurons like microglia (Liu et al., 2020). In addition, brain degeneration in Parkinson's Disease is mainly caused by α-synuclein which has then shown to be reduced by intracerebral injection of AAV vectors to prevent the excessive expression of EB components. The process is done by stimulating axon and neuron survival which is directly correlated with autophagy and production of lysosomes (Chen et al., 2020). Moreover, another innovative approach for the treatment of Parkinsons is dopaminergic cell transplant. This is done to revive the function of dopamine by stem cell regeneration. When neurons of the midbrain are transplanted into the corpus striatum which is then approached by stem cells. Fetal midbrain transplantation has also shown promising results in elevating symptoms (Liu et al., 2020).

Neurosurgical Interventions: Advances in Deep Brain Stimulation and Beyond

The latest approach for the treatment of Parkinson's Disease is deep brain stimulation. The technique involves laceration and delivery of dopaminergic drug, which produces the following aftermath of motor circuit excitation that is targeted, as well as consistent delivery of dopaminergic drug can reduce motor issues (Sharma et al., 2020). Deep brain stimulation modifies neuronal activity by placing tiny electrodes in certain brain areas for the management of movement-related illnesses like Parkinson's disease. Medical professionals can modify the outcome and relieve symptoms like tremors and muscular stiffness by connecting these electrodes to a waveform generator that is positioned beneath the surface of the skin in the chest (Zhang et al., 2024).

Numerous extensive randomized controlled trials have repeatedly demonstrated that deep brain stimulation enhances the standard of life, lowers motor limitation scores, and improves daily active duration without dyskinesia as compared to medical intervention alone (Mitchell et al. 2020). Therefore, Deep Brain Stimulation is one surgical procedure that has been authorized to treat Parkinson's induced tremors. As it stimulates particular areas of the brain, including the Globus Pallidus Interna and the Ventral Intermediate Nucleus (Mahboob et al., 2024). In addition, Repetitive transcranial magnetic stimulation (rTMS) is a safe therapy that stimulates brain neurons using fields of magnets. The possibility of using rTMS to treat Parkinson's disease has recently been investigated and it has demonstrated that regular rTMS administered to the primary motor cortex, specifically the foot region, increases walking time in individuals with Parkinson's disease (Harsanyiova et al., 2020). For movement disorders, MRI-guided focused ultrasound (FUS) is a new therapy option. With this method, particular brain regions are targeted by an MRI-compatible ultrasound transducer, which progressively increases the sound intensity to attain burning temperatures. While MRI thermometry guarantees precise lesion implantation, patient tremor assessments are used to gauge the efficacy of the lesion throughout the treatment (Mitchell et al., 2020).

Brain-Computer Interfaces and Neural Prosthetics

The translation of brain impulses into actions is made possible by brain-computer interface technology, which improves innate capacities and provides patients with neurological diagnoses with cutting-edge rehabilitation and therapy choices. It has great promise for the diagnosis, therapeutic intervention, and rehabilitation of many neurological disorders (Zhang et al., 2024). Another invasive technology is motor neuroprocessing which can read brain impulses, stimulate specific parts of the brain, and connect to other devices. The two main types of these therapies are replacement, which replaces lost activities, and repair, which tries to restore or enhance pre-existing motor functions (Veltink, 2021).

Lifestyle and Physical Therapy

As Parkinson's disease worsens, patients frequently have decreased nutritional status and weight loss. Rehabilitation, mortality, and quality of life may all be significantly impacted (Breasail et al., 2022). Sleep disruptions may be a contributing factor to the higher calorie intake, decreased protein intake, and predilection for sugary foods seen in PD patients. It is necessary to investigate the relationship involving sleep and nutrition in individuals with Parkinson's disease (Dunk et al., 2023). Antioxidant vitamins, such as β-carotene, C, E, and A, are essential for shielding cells from the harm that free radicals may do. Because of this, there is a lot of interest in determining if consuming more of these essential elements lowers the probability of Parkinson's disease (Breasail et al., 2022)

In individuals with Parkinson's disease, more physical activity via a more active lifestyle or involvement in workout and physiotherapy courses has been demonstrated to improve physical fitness as well as psychological and motor function (Bouça et al., 2020). In addition to being frequently used to help patients with Parkinson's disease with their motor symptoms, physical therapy, and exercise have also been studied for their effects on controlling pain. These treatments have demonstrated some promise, especially in the treatment of musculoskeletal pain. Physical and therapeutic therapies were found to be the most effective in reducing pain in a poll study of patients with Parkinson's disease, although the relief was frequently short-lived (Edinoff et al., 2020). In addition, exercise helps in increasing dopaminergic propagation and communication. This further helps individuals with neurodegeneration disorder as it helps enhance brain connection and improve behavioral effects (Saluja et al., 2023). Furthermore, the GABAergic mixed neurons can further improve the function of the brain by elevating the synaptic regeneration and development when the brain-derived neurotrophic factor is increased. Active exercise and regular physical activity have proven to help in balance, and improve gait patterns, and overall motor functions. Therapies such as dancing, aqua therapy, and yoga are helpful in Parkinson's Disease (Lee et al., 2024*)*. Individuals who took part in a research study have claimed to see visible improvement about the group that did not partake, after seven weekly sessions. Muscle rigidity discomfort, tiredness, and movement difficulties all had significantly lower visual analogue scale scores. Furthermore, stride length and gait speed were markedly enhanced (Radder et al, 2020). In addition to increasing mobility and general motor function, biomechanical techniques can help patients with non-motor symptoms including pain and a fear of falling. Instead of serving as a specialized therapy for physical activity, these techniques can be used in conjunction with therapies that focus on the fundamental pathophysiology of the condition (Gandolfi et al., 2024). According to a study, aqua therapy, especially when it uses hot water, can lessen one's impression of pain by making free nerve endings less sensitive. The tension on the muscles is reduced, and the amplitude of movement is maintained or enhanced. Furthermore, the water immersion's sensory stimuli effectively interrupt the pain process by competing with unpleasant stimuli (Henemann et al, 2023). The beneficial effects of exercise therapy on motor functioning have been demonstrated by their considerable improvement of motor symptoms and improvement of activities of daily living in people with Parkinson's disease (Choi et al., 2020). Patients with Parkinson's disease should engage in about 150 minutes per day of moderate-intensity physical activity. Most individuals with Parkinson's disease cannot adhere to these rules (Bouça et al., 2020).

Patient-Centered Care

As the disease progresses, the complexity of care increases, leading to a loss of independence in day-to-day tasks and the requirement for ongoing assistance. This can hurt the caregiver as well as it requires their persistent personal investment and can alleviate stress (Cianfrocca et al., 2020). Routine tasks such as bathing, changing, eating, cooking, and as simple as locomotion require the assistance of a caregiver for those diagnosed with Parkinson's (Modugno et al., 2020). Furthermore, the rate of depression is higher in patients with Parkinson's which further causes a lower satisfactory impression of life which as a results leads to further duties for the caregiver. In people with Parkinson's disease, higher incidences of depressive disorders and poor reported satisfaction with life lead to a greater caregiver burden. Qualities of the caregiver, such as their psychological well-being, perspective on life, and the grief brought on by the illness, are also associated with higher loads. With regard to many studies, how far the disease has progressed, the level of disability and the psychological well-being of the patient affect the burden of the caregiver (Macchi et al., 2020).

Psychological conditions but not limited to depression, cognitive inability, and sleep disorder are very common in individuals with Parkinsons. These elements have the potential to drastically degrade the standards of life (Zhao et al., 2021). As the disease worsens, mental decline is a typical symptom, and a predilection for sweet foods is associated with particular impairments in frontal lobe function. This is consistent with the executive dysfunction frequently observed in PD. Increased reliance on other people for food intake is a risk contributing to cognitive deterioration as it progresses. Due to motor limitations, patients are possibly less likely to request food or to physically prepare and get it, especially in unfamiliar situations like care facilities (Breasail et al., 2022). The frequency of depression in people with Parkinson's disease is greater when compared with the general population, at approximately one-third. Depression was shown to be significantly associated with disability, small illness progression effect, and mental decline. The idea that depression is the most significant marker of satisfaction with life and that it adds to the burden of disease is supported by this (Burchill et al., 2024). In addition to meeting social and emotional requirements and maybe increasing adherence, centered around community group balancing training programs for people with early-stage Parkinson's disease have been shown to enhance self-reported balance control (Aye et al., 2020). By addressing restrictions in walking, manual chores, and self-transfers that affect day-to-day functioning, occupational therapy (OT) enhances physical therapy. OT

includes techniques like schedule planning and environmental adjustments to enable people to participate in activities in a meaningful way, whereas physical therapy concentrates on mobility. Self-assessed performance of everyday chores can be enhanced by home-based occupational therapy sessions (Lee et al., 2021). Physical rehabilitation should be taken into consideration in addition to traditional medication and cutting-edge therapies like deep brain stimulation in order to enhance the standard of life in the functional domain (Zhao et al., 2021).

Future Directions

Although machine learning systems are still in their infancy and are subject to biases, mistakes, and traps, they are now capable of automatically analyzing and classifying radiological and clinical data related to Parkinson's disease. For example, since clinical Parkinson's diagnosis has a considerable mistake rate, labeling training data based on the practitioner's judgment may result in errors (Zhang, 2022). Recognized for their enduring effectiveness, therapeutic robots may help individuals with certain functional motions on their own and offer a numerical evaluation of their progress throughout rehabilitation. Notably, people suffering from gait abnormalities brought on by diseases including stroke, spinal cord injury, and Parkinson's disease have found that Robot-Assisted Gait Training is a useful tool for helping them rehabilitate (Harsanyiova et al., 2020). Furthermore, in chronic individuals with stroke, their motor function has been shown to improve with virtual reality (VR) training. VR technology may give individuals with Parkinson's a secure and efficient setting to exercise and recover. Robotic machine-assisted rehabilitation also helps patients improve their motor results by functioning as a force multiplication for traditional training and rehab (Yau et al., 2024). Given that many neurological test results are visual, telemedicine is very useful in evaluating those diagnosed with Parkinson's disease and other neurological conditions that affect movement. To determine suitability for advanced Parkinson's therapy, certain parts of the neurological assessment can be performed during phone consultations, with findings that are equivalent to those of in-person evaluations (Cubo et al., 2022). Lastly, one possible future therapy for Parkinson's disease is cell transplantation. The use of homozygous and heterozygous cells, such as pluripotent stem cells grown artificially and human embryonic stem cells, has been investigated in trials (Lee et al., 2021).

Conclusion

Parkinson's disease is a complex neurodegenerative disorder that significantly impacts motor and non-motor functions. It arises due to the progressive loss of dopamine-producing neurons in the substantia nigra, leading to hallmark symptoms such as tremors, rigidity, bradykinesia, and postural instability. Despite its challenges, advancements in understanding the pathophysiology, genetics, and environmental factors contributing to PD have paved the way for better diagnostic tools and treatment options. Currently, treatment focuses on symptom management through medications like levodopa, dopamine agonists, and advanced therapies such as deep brain stimulation. Ongoing research into neuroprotective strategies, biomarkers for early detection, and novel therapeutic approaches offers hope for slowing or even halting disease progression in the future. Supportive care, including physical therapy, occupational therapy, and mental health resources, is vital in enhancing the quality of life for individuals with PD and their caregivers. While there is no cure yet, a multidisciplinary approach and continued research hold promise for improved outcomes and, ultimately, a cure for Parkinson's disease.

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