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Recent Development in the Treatment of Parkinson's Disease

Pooja Rani, Rohit Kumar*

Assistant Professor, Department of Pharmacy, Krishna Institute, Bijnor

Email Id-rohitkumar.rke2012@gmail.com

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ABSTRACT

Independent of race or social class, Parkinson's disease (PD) affects between 15-25% of old people over the age of 60 and 4% of those over the age of 80. It is the second most prevalent neurogenerative illness in the elderly population. The brain area of the substantianigra, where dopamine (DA) is synthesized, is where Parkinson diseases brought on by the necrosis of dopaminergic neurons, which decrease the amount of dopamine in the synaptic cleft. Dopamine degradation by the Monoamine oxidise B (MAO_B) promopte4s glutamate build up and oxidative stress with the generation of free radicals, which result in excitotoxicity. The diagnosis of PD is determined by examining the motor symptoms because there is no laboratory test, biomarkers, or imaging investigation anti-cholinergic, dopaminergic agonist. There is known cure for the disease, these medication help patients live longer and function more normally.

KEYWORDS: *Parkinson's disease, Dopamine, Causes, Diagnosis, Symptoms, Pathology, Etiology*

INTRODUCTION:

Parkinson disease is a brain disorder that cause unintended or uncontrollable movement. Such as shaking, stiffness, and difficulty with balance coordination. The clinical syndrome, described by James Parkinson in his 1817 'Essay on the shaking palsy', And commonly referred to as 'Parkinson's disease' (PD), is characterised by the cardinal feature4s of rest tremor, brady kinesia, rigidity and postural instability, and a variety of other motor and non-motor symptom. Neurological disorders are now the leading source of disability in the world, and PD is the fastest growing of these disorders. The Global Burden of Disease of Disease in the Study estimates that the number of PD case will double from about 7 million in 20158 to about 13 million in 2040, suggesting a potential 'PD Pandemic', While this extrapolation based on future growth of population is just an estimate, it highlights the enormous burden that PD and related neurodegenerative conditions can pose for society. Major milestones in PD etiopathogenesis include the identification of intra-cytoplasm inclusion bodies ('Lewy boldies') as a pathologic hallmark by Frederick Lewy in 1912 and the discovery of dopamine deficiency and its involvement in the Parkinson an animal models. The pioneering work of Arvid Carlsson and Oleh Hoornykiewicz starting in 1957 established the link between dopamine deficiency

and PD. The latter was supported by the proof of concept demonstrating clinical rescue in the first trial in PD patients with intravenous levodopa in 1961 and the introduction of high dosage levodopa therapy by George Cotzias in 1967 [1-3].

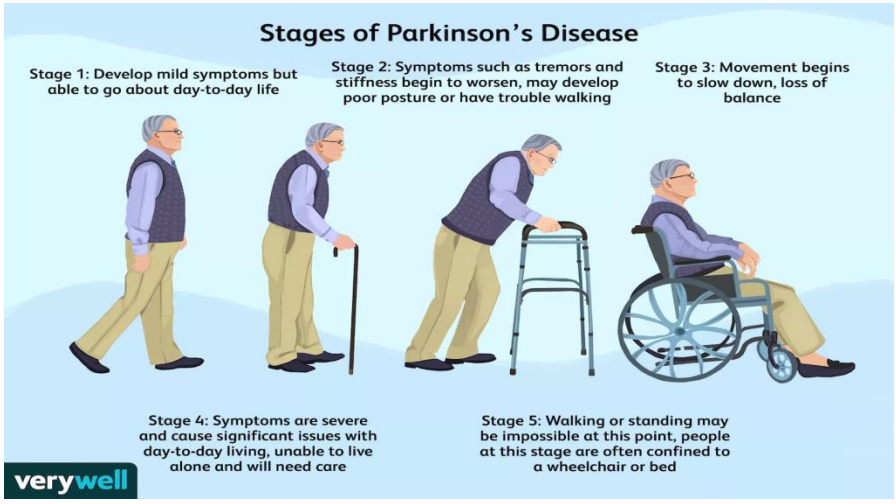


Fig.1: Stages of Parkinson's disease

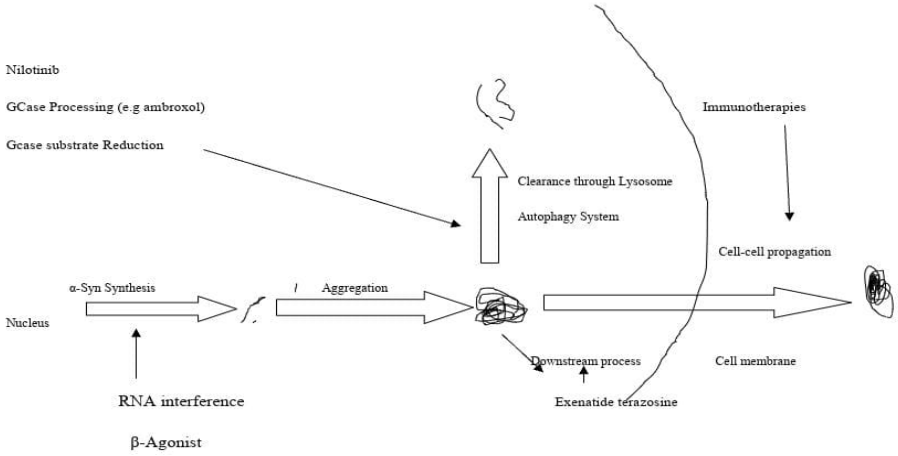


Fig.2: Putative disease modifying therapies for PD

CAUSES:

IN 1982, William Langston, a neurologist, described seven patients in the San Francisco Bay Area who were using 'synthetic heroin' and developed Parkinsonism, features. Subsequent investigations revealed the cause of this drug-induced Parkinsonism, 1-methyl-4 phenyl-1, 2, 3, 6-tetrahydropyridine, which is toxic to substantial nigra dopaminergic neurons. The discovery had a remarkable impact on research into the etiopathogenesis of PD and experimental therapeutics, leading to drug trials in animal models and large-scale epidemiological studies on occupational exposure to potential toxins. The clinical criteria of the UK Parkinson's Disease Society Brain Bank for probable PD require the presence of bradykinesia and one of the following features: Hz rest tremor, or postural instability; in addition, three supportive feature are required [4].

The International Parkinson's and Movement Disorder Society (MDS) developed their own clinical diagnostic criteria that include presence of Parkinsonism (bradykinesia plus either rest tremor or rigidity); absence of absolute exclusionary criteria, supportive criteria and no red flags. In addition to variety of clinical rating scales, particularly the Unified Parkinson's Disease Rating Scale (UPDRS) used to assess severity of the disease, reliable diagnostic, pre-symptomatic and progression biomarkers are being developed to support the diagnostic, to track the course of the disease [5].

The term 'prodromal' PD refers to a phase (up to 15-20 years before onset of motor symptoms during which clinical signs of disease are not evident but underlying neurodegeneration has started and

progressed (figure1). Clinical studies have shown that rapid eye movement sleep behaviour disorder (RBD), depression, olfactory dysfunction, constipation and autonomic dysfunction may be present during this period. The 2019 Movement Disorders Society diagnostic criteria for proteomic PD have added other new markers (such as diabetes mellitus and physical inactivity), facilitating a web-based calculation of prodromic risk. The list of potential clinical, biochemical, imaging and genetics risk markers will likely continue to increase in the future. Numerous risk factors and genetic mutations are associated with PD. Risk factors for the disease includes oxidative stress, the formation of free radicals, and a number of environmental toxins (Table.1). Limited data support genetic associations with PD, with some gene mutations identified (Table.2). Interestingly, an inverse relationship exists between cigarette smoking, caffeine intake, and the risk of developing PD. Inhibition of the enzyme monoamine oxidase (MAO) may explain the protective effects of tobacco smoking, whereas the benefits of caffeine may be related to its adenosine antagonist activity. The variable prevalence of PD throughout the world suggests that environmental and genetic factors along with ethnic differences may all play a role in disease pathogenesis. Biomedical research in individuals with PD continues and may help to indentify additional risk factors and to guide future prevention and treatment decisions [6-9].

Table.1: Risk Factors Associated With Parkinson's disease [10-11]

Risk Factor	Description
Age	Risk increases with advancing age
Genetics	Family history and genetic mutations such as SNCA, LRRK2, PARK2, PINK1, and DJ1
Environmental Toxins	Exposure to pesticides, herbicides, solvents, and heavy metals such as manganese and lead
Head Trauma	History of head injuries or concussions
Rural Living	Living in rural areas with potential exposure to agricultural chemicals
Gender	Men have a slightly higher risk than women
Smoking	Some studies suggest smoking may reduce the risk, but long-term health effects outweigh benefits
Caffeine Intake	Higher caffeine consumption may have a protective effect
Anti-inflammatory Medications	Some evidence suggests nonsteroidal anti-inflammatory drugs (NSAIDs) may lower the risk
Depression and Anxiety	Mental health conditions may precede Parkinson's or exacerbate symptoms
Low Vitamin D Levels	Low levels of vitamin D have been associated with a higher risk

Table.2: Gene Mutations Associated with Parkinson's disease [13-14].

Gene Mutation	Associated Protein	Function	Implication in Parkinson's Disease
SNCA	Alpha-synuclein	Protein aggregation	Mutations can lead to abnormal aggregation of alpha-synuclein, a hallmark of Parkinson's pathology
LRRK2	Leucine-rich repeat	Regulation of	Mutations in LRRK2 are the most common

	kinase 2	cellular processes	cause of familial Parkinson's disease
PARK2	Parkin	Ubiquitin ligase activity	Loss-of-function mutations impair protein degradation pathways
PINK1	PTEN-induced kinase 1	Mitochondrial function regulation	Mutations disrupt mitochondrial quality control and lead to cell death
DJ1	Protein deglycase DJ-1	Antioxidant activity	Loss-of-function mutations increase oxidative stress and cell vulnerability
GBA	Beta-glucocerebrosidase	Lysosomal function regulation	Mutations increase alpha-synuclein aggregation and decrease lysosomal activity
ATP13A2	ATPase cation transporting 13A2	Cation transport across membranes	Mutations impair lysosomal and mitochondrial function, leading to cell death
VPS35	Vacuolar protein sorting-associated protein 35	Protein trafficking	Mutations disrupt protein trafficking within cells, contributing to neurodegeneration
EIF4G1	Eukaryotic translation initiation factor 4 gamma 1	Protein synthesis	Mutations affect protein synthesis, leading to cellular dysfunction

DIAGNOSIS:

The differential diagnosis of PD should include a comprehensive history and physical examination. Difficulty or questionable case should be referred to a movement disorder Specialist for further evaluation. There is no definitive test to confirm the diagnosis of Parkinson disease. Therefore a clinical diagnosis requires the clinician to review the patient's history to assess symptoms, and to rule out alternative diagnosis such as multiple system atrophy, DLB disease and essential tremor [15-16].

Table.3: Disease and condition that may require differentiation from Parkinson disease

Disease/Condition	**Clinical Features**	**Differential Diagnosis**
Essential Tremor	Tremor primarily during movement, may involve hands, head, voice	Differentiated by absence of other Parkinsonian features such as rigidity and bradykinesia
Drug-induced Parkinsonism	Onset of symptoms after exposure to dopamine-blocking drugs	Symptoms may improve upon discontinuation of offending medication; similar to Parkinson's but with a clear medication history
Multiple System Atrophy (MSA)	Autonomic dysfunction, cerebellar signs, and parkinsonism	Progressive autonomic failure, cerebellar ataxia, and parkinsonism; distinct from Parkinson's in its rapid progression
Progressive Supranuclear Palsy (PSP)	Vertical gaze palsy, postural instability, and falls	Early falls, vertical supranuclear gaze palsy, and axial rigidity; often differentiated by the absence of resting tremor
Dementia with Lewy Bodies (DLB)	Fluctuating cognition, visual hallucinations, and REM sleep behavior disorder	Cognitive decline, visual hallucinations, and REM sleep behavior disorder; may have overlapping features with Parkinson's
Vascular Parkinsonism	History of stroke or cerebrovascular	Parkinsonism following a stroke or evidence of

	disease	cerebrovascular disease on imaging; symptoms may improve with vascular treatment

The clinical motor features of PD described as the classical traids include a 4-Hz to 6-Hz resting tremor,"COGWHEEL" rigidity and bradykinesia (TABLE.4) . These cardinal features often reported as the first clinical finding of the disease. A fourth feature postural instability occurs in approximately 50%of PD patients within five years of diagnosis [17].

TABLE.4: Motor Symptoms of Parkinson Disease

Motor Symptoms	Description
Bradykinesia	Slowness of movement, including difficulty initiating and executing voluntary movements
Tremor	Typically a resting tremor, most commonly affecting hands, fingers, or thumbs
Rigidity	Increased muscle tone leading to stiffness and resistance to passive movement
Postural Instability	Impaired balance and coordination, leading to difficulty maintaining an upright posture
Gait Disturbances	Shuffling gait, reduced arm swing, and festination (short, shuffling steps)
Freezing of Gait	Brief episodes where the feet seem to stick to the floor, making it difficult to start walking

SYMPTOMS:

Further complicating an early diagnosis is the presence of no motor co morbidities, including Depression, Anxiety, Fatigue, Constipation, Anosmia, and Sleep disorder which is the clinician may not recognize as being associated with Parkinson disease [18].

Table.5: Symptoms of Parkinson disease [19-20].

Symptom	Description
Tremor	Involuntary shaking, typically starting in one hand, often occurring at rest
Bradykinesia	Slowness of movement, including difficulty initiating and performing voluntary movements
Rigidity	Stiffness or inflexibility of muscles, often leading to joint pain and limited range of motion
Postural instability	Impaired balance and coordination, leading to difficulties in maintaining an upright posture
Gait disturbances	Changes in walking pattern, such as shuffling steps, reduced arm swing, and difficulty turning
Freezing of gait	Brief episodes where the feet seem to stick to the ground, making it challenging to start walking

TABLE.6: Non-motors Symptoms of Parkinson disease [21].

Non-motor Symptoms	Description
Hyposmia	Reduced sense of smell, often occurring early in the disease progression
Constipation	Difficulty passing stools, often due to reduced gastrointestinal motility
Sleep disturbances	Including insomnia, fragmented sleep, excessive daytime sleepiness, and REM sleep behavior disorder
Mood changes	Such as depression, anxiety, apathy, and irritability
Cognitive impairment	Including difficulties with memory, executive function, attention, and visuospatial skills
Fatigue	Persistent tiredness or lack of energy

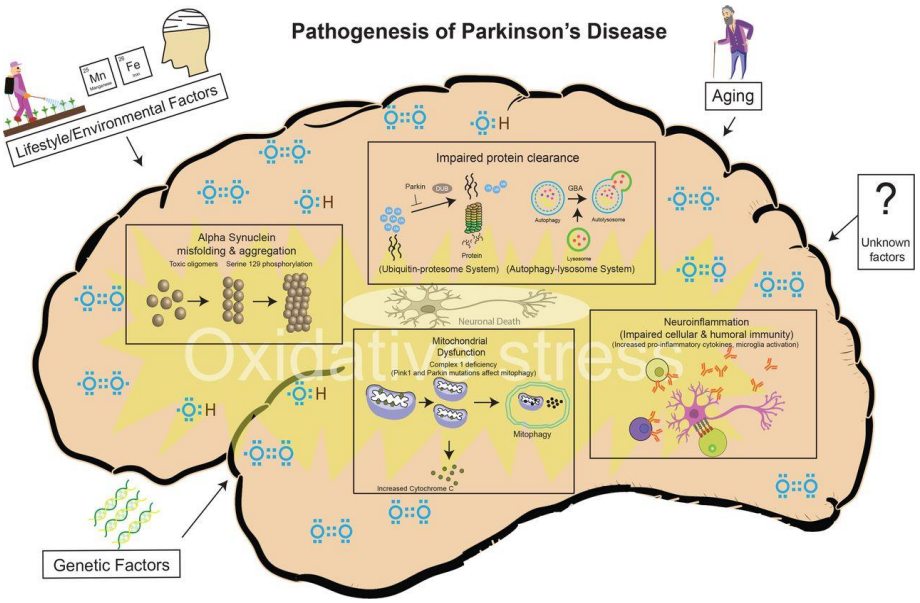
Orthostatic hypotension	Drop in blood pressure upon standing, leading to dizziness or light headedness
Urinary dysfunction	Such as urgency, frequency, nocturia, and incontinence
Sexual dysfunction	Including erectile dysfunction in men and decreased libido in both men and women
Speech and swallowing difficulties	Such as soft speech, monotone voice, and difficulty chewing and swallowing

PATHOLOGY OF PARKINSON DISEASE:

Parkinson's disease (PD) is characterized by the progressive degeneration of dopaminergic neurons in the substantia nigra pars compacta (SNpc) region of the brain, leading to a deficiency of dopamine, a neurotransmitter crucial for motor control. The exact cause of this neurodegeneration remains elusive, but a combination of genetic and environmental factors is believed to contribute to its pathogenesis.

One prominent pathological hallmark of PD is the presence of intracellular protein aggregates known as Lewy bodies, primarily composed of alpha-synuclein. These abnormal protein accumulations disrupt cellular function and lead to neuronal dysfunction and eventual cell death. Additionally, oxidative stress, mitochondrial dysfunction, Neuroinflammation, and impaired protein clearance mechanisms further exacerbate neurodegeneration in PD [22].

The pathological process of PD is not limited to the substantial nigra but also involves other brain regions, including the basal ganglia, cortex, and brainstem. Neurotransmitter imbalances, particularly involving dopamine, acetylcholine, and glutamate, contribute to the motor and non-motor symptoms observed in PD [23-24].



Advance in Deep Brain Stimulation:

Deep Brain Stimulation (DBS) has emerged as a revolutionary treatment modality for Parkinson's disease (PD) and other movement disorders. Recent advances in DBS technology have significantly improved its efficacy, safety, and therapeutic outcomes. One notable advancement is the development of directional leads, allowing for more precise targeting of specific brain regions implicated in PD pathophysiology. Directional leads offer greater flexibility in steering the electrical field, thereby minimizing side effects and maximizing therapeutic benefits. Additionally, advancements in imaging techniques, such as intraoperative MRI and tractography, enable real-time visualization and accurate placement of DBS electrodes, enhancing procedural precision and patient outcomes [25-26].

Moreover, the introduction of closed-loop or adaptive stimulation systems represents a significant breakthrough in DBS therapy. These systems incorporate feedback mechanisms that adjust

stimulation parameters in response to changes in neural activity, optimizing treatment efficacy and minimizing adverse effects. Furthermore, ongoing research explores novel stimulation targets beyond the traditional basal ganglia circuitry, including the pedunculopontine nucleus and the sub thalamic nucleus, offering promising avenues for expanding the therapeutic repertoire of DBS in PD management [27].

Regenerative treatments

Pharmacological approaches describes above there is consider interest in the use of cell based and gene therapies to replace the function of the lost dopaminergic neurons. Gene therapy may be used to increase dopamine levels in the striatum .Tyrosine hydroxylase are needed for the production of the dopamine precursor levodopa. Voyager therapeutics has developed an adeno-associated virus therapy containing the gene for AADC [28].

ETIOLOGY OF PARKINSON DISEASE:

Parkinson's disease (PD) is a complex neurodegenerative disorder characterized by the progressive loss of dopaminergic neurons in the substantial nigra region of the brain. While the exact etiology of PD remains elusive, it is widely believed to involve a combination of genetic susceptibility, environmental factors, and aging-related changes in neuronal function. Genetic factors play a significant role in PD, with mutations in several genes implicated in the familial form of the disease. The most well-known genetic risk factor is mutations in the PARKIN gene, which is associated with autosomal recessive juvenile Parkinsonism. Other genes linked to familial PD include SNCA, encoding alpha-synuclein, whose abnormal aggregation forms Lewy bodies, a pathological hallmark of PD. Mutations in LRRK2, PINK1, and DJ-1 genes also contribute to familial PD cases, each affecting different cellular pathways involved in mitochondrial function, protein degradation, and oxidative stress response. Environmental factors such as exposure to pesticides, herbicides, heavy metals, and certain toxins have been implicated in increasing the risk of developing PD. Chronic exposure to these environmental toxins may trigger oxidative stress, mitochondrial dysfunction, and inflammation, leading to neuronal damage and eventual cell death [29-30].

Age is the most significant risk factor for PD, with the prevalence of the disease increasing with advancing age. Age-related changes in cellular mechanisms, including impaired protein degradation, mitochondrial dysfunction, and increased oxidative stress, may contribute to the progressive degeneration of dopaminergic neurons [31].

Furthermore, emerging evidence suggests that Neuroinflammation, dysfunction of the ubiquitin-proteasome system, and disruptions in autophagy pathways may also play crucial roles in the pathogenesis of PD. Additionally, recent research has highlighted the involvement of gut-brain axis dysfunction and symbiosis of the gut micro biota in PD pathophysiology, suggesting a potential link between gastrointestinal health and neurodegeneration [32].

Overall, the etiology of PD is multifactorial, involving intricate interactions between genetic susceptibility, environmental exposures, aging-related changes, and various cellular mechanisms. Understanding these complex interplays is essential for developing targeted therapeutic interventions and disease-modifying strategies to effectively treat and potentially prevent Parkinson's disease [33-37].

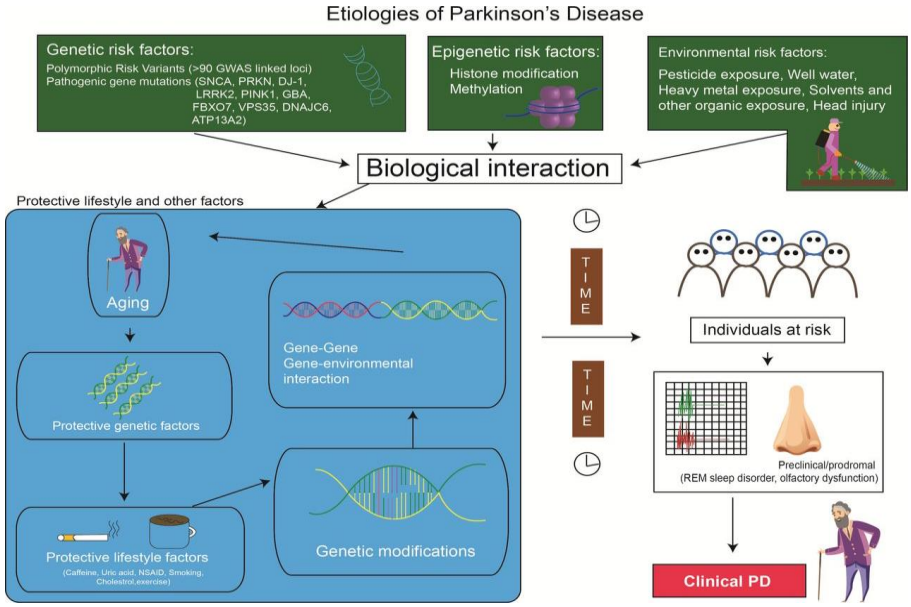


Fig.4: Etiology of Parkinson disease

Conclusion:

Recent advancements in Parkinson's disease treatment signify a paradigm shift towards more effective symptom management and disease modification. The introduction of novel pharmacotherapies, including selective dopamine agonists and levodopa-carbidopa intestinal gel, has revolutionized symptom control, providing smoother motor function and reduced side effects. Emerging therapies targeting non-dopaminergic pathways offer hope for addressing non-motor symptoms and slowing disease progression. Additionally, research into neuroprotective strategies such as gene therapy and stem cell transplantation holds promise for preserving dopaminergic neurons and potentially reversing neurodegeneration. Personalized medicine approaches tailored to individual patient profiles enhance treatment efficacy and minimize adverse effects. Non-pharmacological interventions, including deep brain stimulation and multidisciplinary care, play vital roles in managing motor and non-motor symptoms, improving quality of life, and supporting overall well-being. In conclusion, recent developments in Parkinson's disease treatment represent significant progress towards more holistic, personalized, and effective approaches, underscoring the importance of continued research and innovation in the quest for better therapeutic outcomes and ultimately, a cure for this debilitating condition.

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