ISSN (Online): 2455-3662
EPRA International Journal of Multidisciplinary Research (IJMR) - Peer Reviewed Journal
Volume: 10| Issue: 11| November 2024|| Journal DOI: 10.36713/epra2013 || SJIF Impact Factor 2024: 8.402|| ISI Value

A REVIEW ON PARKINSON'S DISEASE- ETIOLOGY, PATHOPHYSIOLOGY AND EMERGING THERAPIES

Bhagyashri KalyanPadul[1*], MR. Abhijeet.Rathod[2], Yogeshwari. B. Pamane[3], Aarti.B. Narwade[4], Pooj. K. Ekhande[5]

[1]Student of Bachelor of Pharmacy, Raosaheb Patil Danve College of Pharmacy, Badnapur, Jalna
[2]Asst.Prof.(Faculty of pharmaceutics) Raosaheb Patil Danve College of Pharmacy, Badnapur, Jalna
[3]Student of Bachelor of Pharmacy, Raosaheb Patil Danve College of Pharmacy, Badnapur, Jalna
[4]Student of Bachelor of Pharmacy, Raosaheb Patil Danve college of Pharmacy, Badnapur, Jalna
[5]Student of bachelor of Pharmacy, Raosaheb Patil Danve College of Pharmacy, Badnapur, Jalna
Raosaheb Patil Danve College of Pharmacy, Badnapur, Jalna 431202

ABSTRACT

More than seven million people worldwide suffer with Parkinson's disease (PD), a common neurological illness that causes a variety of motor and non-motor symptoms due to the death of dopaminergic neurons.

Although the exact cause of Parkinson's disease is still mostly unknown, environmental and genetic factors are thought to be involved. Dopamine is a neurotransmitter that is involved in controlling motivation, memory, locomotion, and other physiological functions.

The death of dopaminergic neurons in Parkinson's disease patients results in a drop in dopamine levels, impairing motor function and maybe contributing to certain patients' cognitive impairments.

The goal of the review is to examine the many facets of Parkinson's disease (PD), including its history, prevalence trends, pathogenesis, difficulties in diagnosing it, and various treatment approaches.

Parkinson's disease is a progressive neurological disorder that manifests as both motor and non-motor symptoms.

Numerous variables, such as aging, heredity, and exposure to specific environmental chemicals, can contribute to Parkinson's disease. Furthermore, oxidative stress, protein aggregation, neuroinflammation, and mitochondrial dysfunction are important factors in the development of Parkinson's disease.

KEY WORDS: *motor dysfunction, neurodegenerative diseases, Parkinson's disease.*

OVERVIEW

Parkinson's disease is a progressive neurological disorder that manifests as both motor and non-motor symptoms. About 1% of people over 60 globally suffer from Parkinson's disease, which is the second most prevalent neurological illness after Alzheimer's disease.

The average beginning of Parkinson's disease is around age 60, and its incidence rises with age. With a male-to-female ratio of about, men are more prone than women to get Parkinson's disease.

In his essay "An Essay on Shaking Palsy," published in 1817, British physician James Parkinson provided the earliest description of Parkinson's disease.

This essay describes Parkinson's observations of six individuals who had tremors, stiffness, and trouble moving. He identified a neurological condition he named "paralysis agitans" as the cause of these symptoms. As more and more cases of this illness were reported during the ensuing decades, the term "Parkinson's disease" gained popularity. The biggest risk factor is aging, but genetics and environmental factors may also influence when the disease manifests.

Approximately 1 to 2 percent of the global population suffers from this neurological condition. Social, cognitive (non-motor), and motor symptoms are all present in Parkinson's disease. Because of their unique characteristics, motor symptoms such bradykinesia, tremors, and rigidity are easily recognized. Cognitive symptoms are becoming more widely acknowledged and are linked to communication and behaviour issues that hinder social interaction.

Among the motor symptoms include tremors, bradykinesia, dyskinesia, motor fluctuations, postural instability, irregularities of gait, and poor turning ability. Lethargy, sleep disorders, constipation, memory problems, and mood swings

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are examples of non-motor symptoms that may appear up to ten years before a diagnosis.Lewy bodies in the midbrain and a depletion of dopaminergic neurons in the substantia nigra are two pathological indicators of Parkinson's disease.

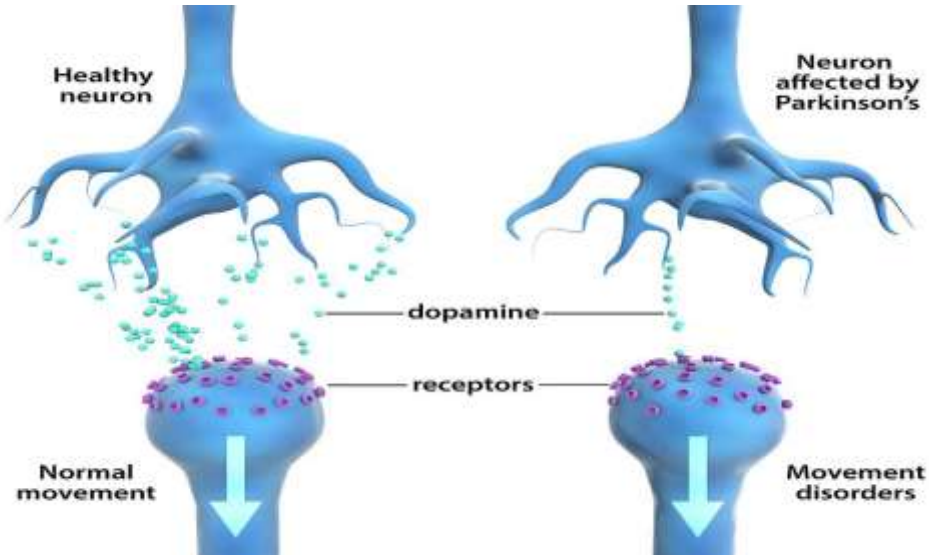


Fig.No.1

Parkinson's disease types include:

Parkinson's disease in its primary form

1. Idiopathic Parkinson's disease: 80–90% of cases are of this type, making it the most prevalent. We don't know what caused it.
2. Familial Parkinson's disease: 5–10% of cases are of this uncommon form. due to mutations in the genes.

Parkinson's disease that develops later

1. Vascular Parkinsonism: This condition is brought on by decreased blood supply to the brain, frequently as a result of small vessel disease or stroke.
2. Drug-Induced Parkinsonism: This condition is brought on by some drugs, including antipsychotics and antiemetic drugs.
3. Toxin-Induced Parkinsonism: This condition is brought on by exposure to toxins such heavy metals and pesticides.

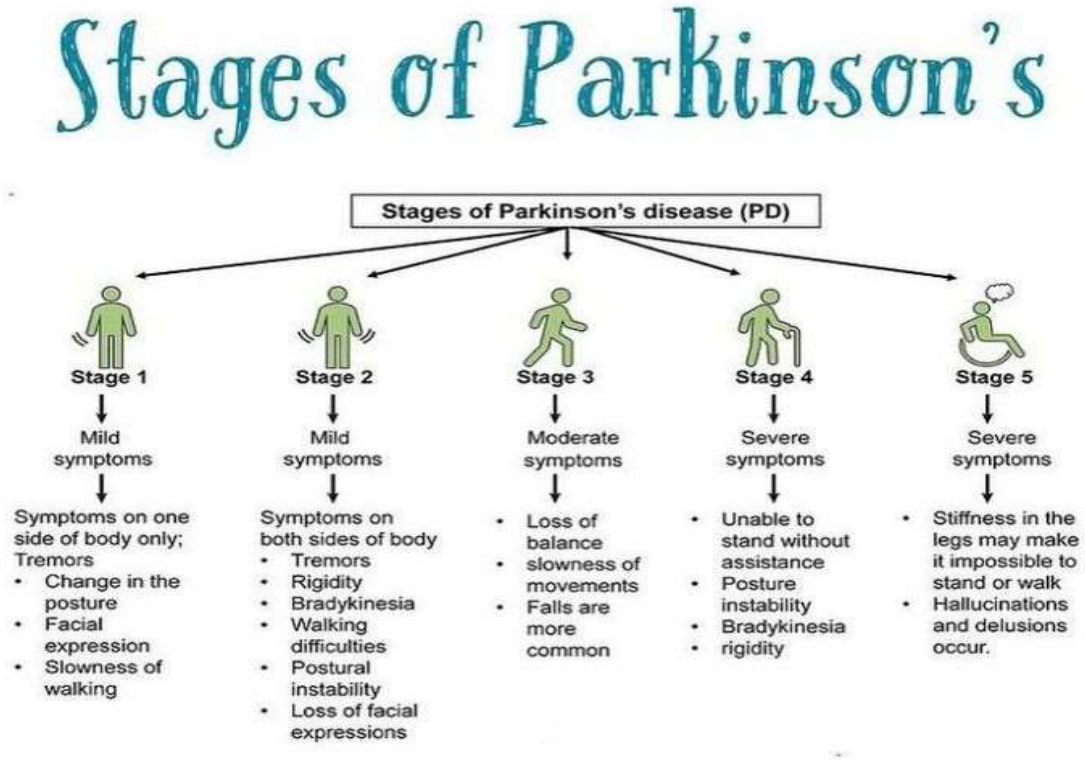


Fig No.2

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What causes Parkinson's disease?
Genetic Contributions: Parkinson's disease in the family

Environmental Aspects:
Exposure to pesticides
Exposure to heavy metals
Air contamination

Lifestyle Factors: Sleep, Exercise, and Diet
Pathophysiology:

Dopaminergic neuronal cell death in the basal ganglia's substantia nigra

Dopaminergic nigrostriatal pathway degeneration

Dopamine storage depletion
An imbalance between the corpus striatum's excitatory (acetylcholine) and inhibitory (dopamine) neurotransmitters

impairment of the extrapyramidal pathways that regulate intricate bodily motions

Bradykinesia, rigidity, and tremors

DIAGNOSIS

A thorough medical history, physical examination, and neurological tests are usually required to diagnose Parkinson's disease. A neurologist can assess a patient's symptoms and rule out other disorders, but there is no specific test for Parkinson's disease.
Pharmacologic management: Creating a disease-modifying treatment that can halt or reduce the neurodegenerative process is the main goal of PD research. To accomplish this goal, there isn't a proven disease-modifying treatment available yet.
Parkinson's disease symptoms include:

Symptoms of the Motor
1. Tremors: Jaw, arm, leg, or hand shaking
2. Rigidity: Muscle rigidity and inflexibility.

Bradykinesia: The inability to move quickly.
4.Postural Instability: Having trouble keeping your posture and balance.

Symptoms Not Related to Motors
1. Cognitive impairment: trouble focusing, remembering, and making decisions.
2. Mood Disorders: mood fluctuations, anxiety, and depression.
3. Autonomic Dysfunction: Inability to control digestion, heart rate, and blood pressure.
4. Sensory symptoms include tingling, pain, and numbness in the arms, legs, and face.

Epidemiology
One percent of adults over 65 have Parkinson's disease (PD), and its incidence and prevalence rise with age. When parkinsonian symptoms appear before the age of forty, it is known as early-onset Parkinson's disease (EOPD). It makes up 3–5% of all instances of PD.

MANAGEMENT AND TREATMENT

While monoamine MAO B inhibitors are only modestly successful in treating bradykinesia and stiffness, dopaminergic treatment is quite beneficial. Levodopa and dopamine agonists aid in slowing the progression of illness and impairment. Trihexyphenidyl and other anticholinergic medications work well for tremor, while dopamine replacement therapy has a weak and erratic effect.

Deep brain stimulation (DBS): is a surgical procedure that has FDA approval and uses implanted electrodes to provide electrical current to different areas of the brain. It turns out to be a safer approach to treating movement abnormalities than ablative techniques, with side effects that are usually reversible if the stimulation is stopped. Although more and more data points to DBS's effectiveness in treating movement disorders, including Parkinson's disease, its underlying mechanisms remain unclear

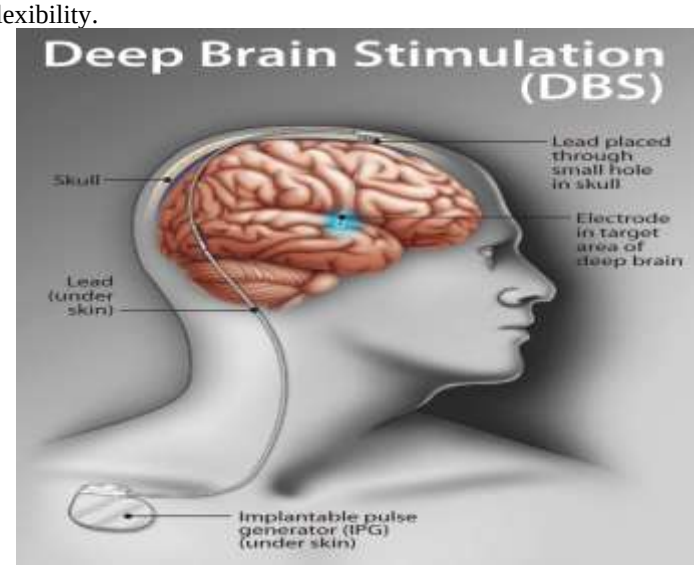


Fig no.3

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The medical procedure of implanting new cells into patients to replace those that have been harmed by illnesses in order to restore the body's compromised function is known as cell replacement therapy.

EMERGING THERAPIES: There is a lot of interest in and debate surrounding new treatment approaches for idiopathic Parkinson's disease, including neurotrophic factors, cell-based therapy, neurotransmitter targeting, and possibly neuroprotective medications. Immunotherapy by vaccination and gene therapy are the most modern treatments for Parkinson's disease.

1. **Cell-Based Treatment**
In recent years, cell-based therapy for Parkinson's disease has advanced significantly. The utilization of fetal ventral mesencephalic (VM) tissue as a source of cells for transplantation was a significant breakthrough.

Gene Therapy
In recent years, gene therapy has emerged as a rapidly growing new discipline. Its fundamental idea is to use adeno-associated viruses or other vectors to deliver DNA, RNA, antisense oligonucleotides, and DNA or RNA editing enzymes to PD patients' brains in order to restore normal gene expression. The amount of vital enzymes involved in dopamine synthesis can be increased by controlling the expression of relevant genes, which will subsequently restore the dopamine content. To increase the survival rate of DA neurons, gene therapy can also offer improved neurotrophic support.

Immunotherapy: Targeting particular proteins implicated in Parkinson's disease with antibodies or vaccinations.

Drugs
1. Levodopa/Carbidopa: Elevates dopamine levels in the brain (Sinemet).
2. Dopamine Agonists: These drugs, such as pramipexole and ropinirole, mimic the effects of dopamine in the brain.
3. MAO-B Inhibitors: These include rasagiline and selegiline, which prevent the brain's dopamine from being broken down.
4. COMT Inhibitors: Prevent the brain from breaking down levodopa (e.g., entacapone, tolcapone).
5. Anticholinergics: Reduce muscle stiffness and tremors (e.g., trihexyphenidyl, benztropine).
6. Amantadine: Enhances motor function and alleviates dyskinesia.

Oxidative stress is the pathogenesis. One of the main pathogenic factors in Parkinson's disease is reactive oxygen species (ROS), which are molecules with oxygen in their molecular composition and highly active chemical properties.

Mitochondrial dysfunction: The primary source of energy for cells, mitochondria are closely related to several physiological functions.

Inflammation Neuroinflammation and intestinal inflammation are two types of inflammation linked to Parkinson's disease. Although neuroinflammation is an immune response that is crucial for safeguarding neurons, it can also harm neurons and accelerate the onset of neurodegenerative illnesses.

Future Views
Finding cures and ways to modify the disease continues to be the main objective of PD research. The emphasis will remain on ways to manage Parkinson's disease (PD) motor symptoms without exacerbating or causing levodopa-induced fluctuations, as well as lowering disability related to symptoms like tremor and gait and balance that are either less responsive to or resistant to levodopa, until such therapies are clinically available.

Therefore, research into non-dopaminergic targets is still important. Basic science studies have consistently shown that aberrant pulsatile dopamine receptor stimulation with numerous post-synaptic non-dopaminergic neurotransmitters and neuromodulatory alterations, specifically affecting glutamate, serotonin, and adenosine, are part of the pathophysiology of levodopa-induced motor fluctuations and dyskinesia.

One of the main things that can restrict translational research is the absence of commercially available medications that can target non-dopaminergic receptors implicated from preclinical investigations.

The purpose of this review is to examine the etiology, pathogenesis, and emerging treatments of Parkinson's disease.

GOALS: 1. To give a summary of what is currently known about the pathophysiology, etiology, and clinical characteristics of Parkinson's disease.
2. To investigate the role of environmental and genetic factors in the development of Parkinson's disease.
3. To investigate novel treatments such as immunotherapy, stem cell therapy, and gene therapy.
4. To examine Parkinson's disease's clinical manifestations and course, encompassing both motor and non-motor symptoms.
5. To determine risk factors

CONCLUSION

Alpha-synuclein aggregation, neurotransmitter imbalance, and dopaminergic neuron loss are the hallmarks of Parkinson's disease, a complex and multifaceted neurodegenerative illness. A complex interaction between molecular, environmental, and hereditary factors contributes to the pathogenesis of Parkinson's disease.

The intricacies of Parkinson's disease and the advancements in our knowledge of its etiology and pathophysiology are highlighted in this study. Current research attempts to address the unmet needs of this debilitating disease, while emerging medicines give hope for bettering patient outcomes.

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