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PARKINSON'S DISEASE: ETIOLOGY, PATHOPHYSIOLOGY AND EMERGING THERAPIES

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ABSTRACT

Parkinson's disease (PD), a prevalent neurodegenerative condition affecting more than seven million individuals globally, manifests through the loss of dopaminergic neurons, leading to diverse motor and non-motor symptoms.[1] The etiology of Parkinson's disease remains largely unknown, but genetic and environmental factors are believed to play a role. The neurotransmitter dopamine is implicated in regulating movement, motivation, memory, and other physiological processes. In individuals with Parkinson's disease, the loss of dopaminergic neurons leads to a reduction in dopamine levels, which causes motor impairment and may also contribute to the cognitive deficits observed in some patients. review aims to explore PD's multifaceted nature, covering its introduction, prevalence patterns, pathophysiology, diagnostic challenges, and varied treatment strategies.[1] Parkinson's disease is a neurological condition that progresses over time and causes both motor and non-motor symptoms.[3] Parkinson's disease is influenced by a variety of factors, including aging, genetics and exposure to certain environmental toxins. Additionally, neuroinflammation, oxidative stress, mitochondrial dysfunction and protein aggregation play pivotal roles in the development of PD.[3]

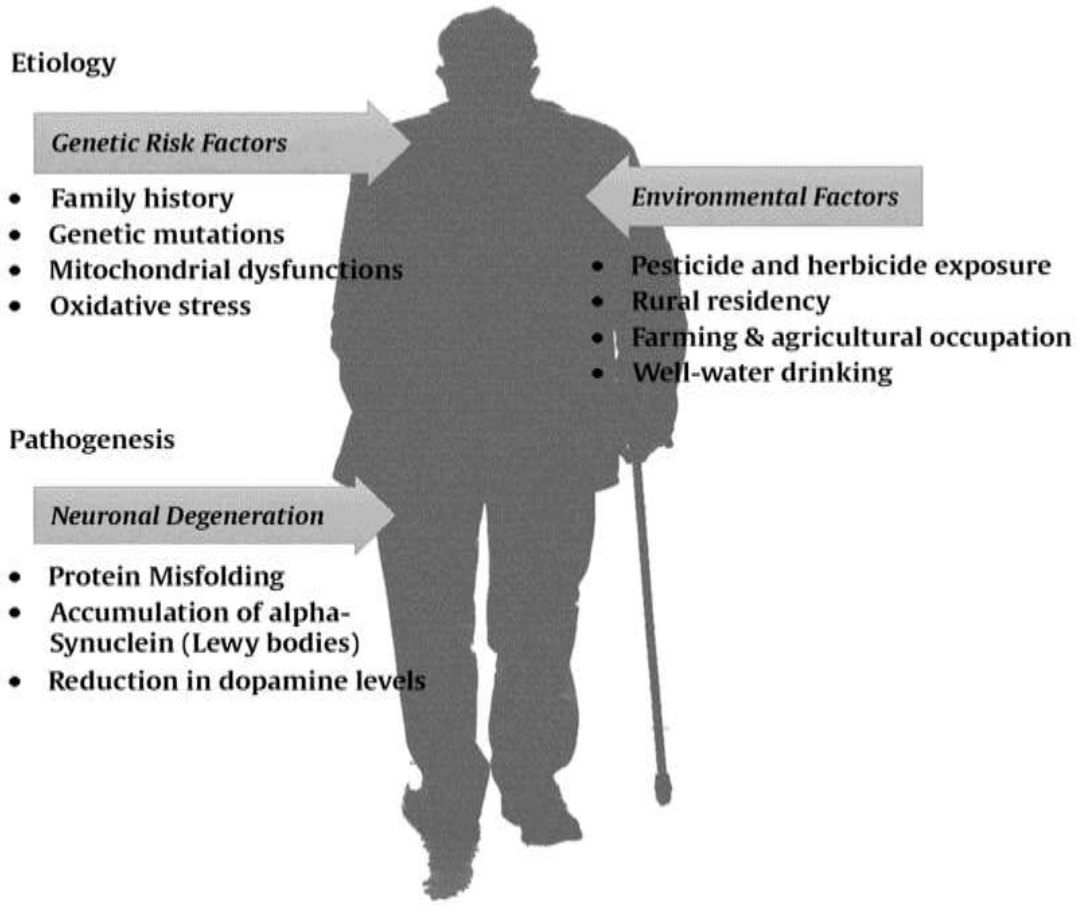
INTRODUCTION

- Parkinson's disease is a neurological condition that progresses over time and causes both motor and non-motor symptoms.[9]
- Parkinson's disease is the second most common neurodegenerative disorder after Alzheimer's disease, affecting approximately 1% of the population over the age of 60 worldwide.[7]

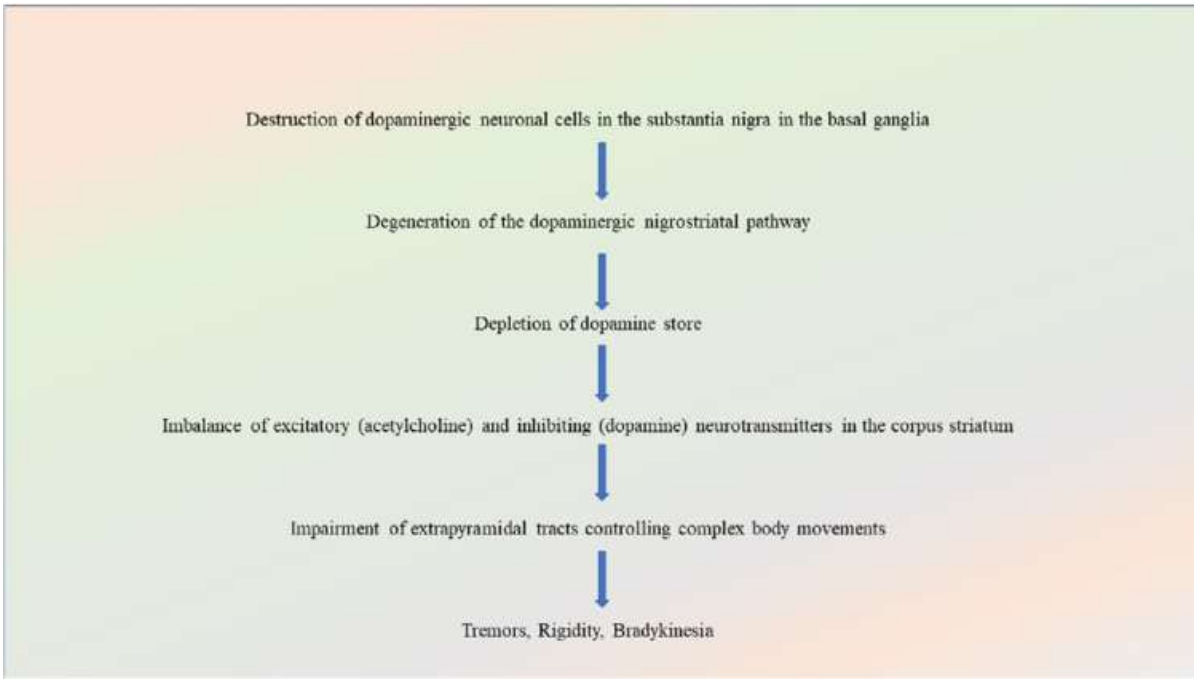
- The incidence of Parkinson's disease increases with age, with a mean onset of around 60 years of age. Compared to women, men are more likely to develop Parkinson's disease, with a male-to-female ratio of approximately.[7]
- Parkinson's disease was first described in 1817 by British physician James Parkinson in his essay "An Essay on Shaking Palsy".[7]
- In this essay, Parkinson observed six patients with symptoms such as tremors, rigidity, and difficulty with movement. He recognized that these symptoms were related to a disease of the nervous system, which he called "paralysis agitans". Over the following decades, more and more cases of this disease were described, and the name "Parkinson's disease" became widely used.
- Aging is the greatest risk factor, but environmental variables and genetics may also have an impact on the onset of the disease.[3]
- About 1% to 2% of people worldwide are affected by this neurological disorder. Parkinson's disease includes motor, cognitive (non-motor) and social symptoms. Motor symptoms such as stiffness, tremors and bradykinesia, are easily identifiable due to their distinctive nature. Cognitive symptoms are increasingly recognized and contribute to behavioural and communication problems that interfere with social interaction.[3]
- Tremors, dyskinesia, bradykinesia, motor f luctuations, postural instability, abnormalities of gait, and poor turning ability are some of the motor symptoms. Non-motor symptoms may precede diagnosis by up to ten years, including lethargy, sleep problems, constipation, memory issues and mood swings.[3]
- Two pathological signs of Parkinson's disease are the presence of Lewy bodies in the midbrain and a loss of dopaminergic neurons in the substantia nigra.[3]

Types of Parkinson's disease

Etiology of Parkinson's disease



PATHOPHYSIOLOGY



The pathophysiology of PD involves loss or degeneration of the dopaminergic neurons in substantia nigra pars compacta (SNpc) and the accumulation Lewy bodies, which are abnormal intracellular aggregates containing proteins, like alpha-synuclein (aSyn) and ubiquitin. About 60-70% of neurons in SNpc are lost before symptoms occur. Research has revealed that the pathogenic process in PD involves regions of the peripheral and central nervous system in addition to the dopaminergic neurons of the SNpc. Lewy body pathology starts in cholinergic and monoaminergic brainstem neurons and in the neurons of the olfactory system, but involves limbic and neocortical brain regions with disease progression. Loss of dopaminergic neurons that was initially restricted to SNpc becomes more widespread by the time end-stage disease has been established.

DIAGNOSIS

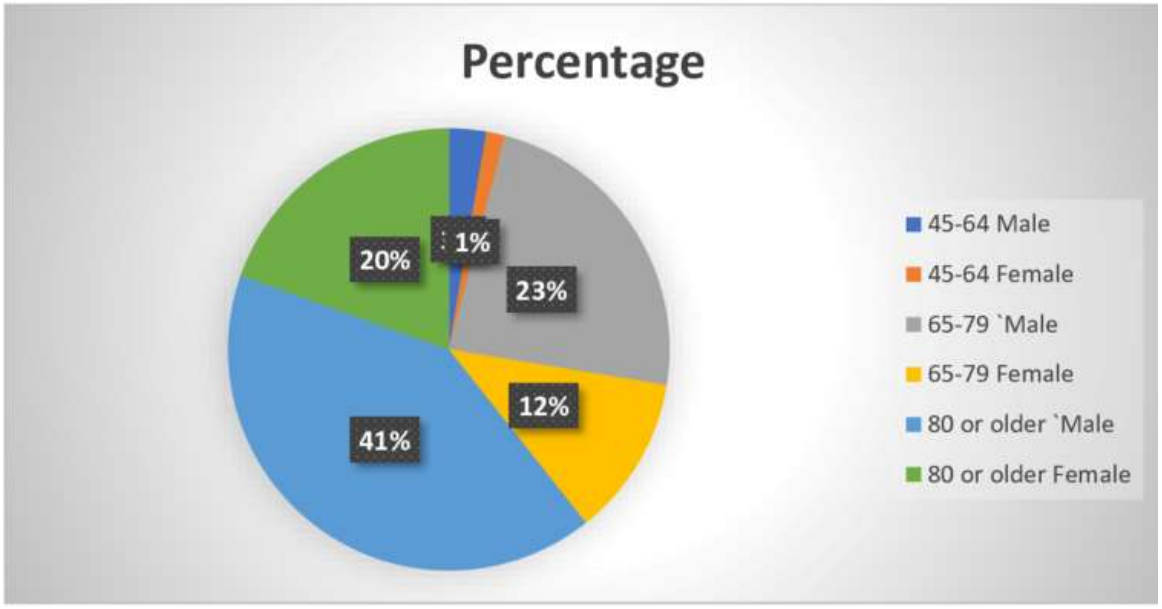
Diagnosis of Parkinson's disease typically involves a through medical history, physical examination, and neurological testing. There is no specific test for Parkinson's disease; however, a neurologist can evaluate a patient's symptoms and rule out other conditions.

Pharmacologic management

The major objective of PD research is to develop disease-modifying therapy that can slow or stop the neurodegenerative process. However, there is no existing definitive disease-modifying therapy to achieve this aim.

Sign and symptoms

Percentage pf prevalence of Parkinson's disease with different age groups



Epidemiology

The incidence and prevalence of PD increases with advancing age, being present in 1% of people over the age of 65 years. Early-onset Parkinson's disease (EOPD) is defined as the onset of parkinsonian features before the age of 40 years. It accounts for 3-5% of all PD cases.[13]

THERAPIES OF PARKINSON'S DISEASE

Dopaminergic therapy is highly effective in bradykinesia and rigidity but monoamine MAO B inhibitors are only moderately effective. Dopamine agonists and levodopa help to reduce disease progression and disability. Tremor responds to anticholinergic drugs like trihexyphenidyl but has a poor and inconsistent response to dopamine replacement therapy.[1]

Deep brain stimulation (DBS)

DBS is an FDA-approved surgical technique whereby electrical current is applied to various parts of the brain via implanted electrodes. In contrast to ablative procedures, it proves to be a safer method in the treatment of movement disorders, producing adverse effects that are generally reversible once the stimulation is terminated. The underlying mechanisms of DBS are not completely understood, although growing evidence supports the efficacy of DBS for the treatment of movement disorders including PD.[10]

Cell replacement therapies

Cell replacement treatment is the medical practice of implanting new cells into patients to replace those that have been damaged by illnesses, hence restoring the body's impaired function

EMERGING THERAPIES

Emerging therapeutic options for treating idiopathic PD, such as neurotrophic factors, cell-based therapy, neurotransmitter targets, and potentially neuroprotective drugs, are generating much interest but also controversy. Most recent treatment options for PD involve immunotherapy through vaccination and gene therapy.[1]

1. Cell-based therapy

Cell-based therapy for PD has shown significant progress in recent years. A major advancement came with the use of fetal ventral mesencephalic (VM) tissue as a cell source for transplantation.[10]

3.3. Gene Therapy

Gene therapy is a rapidly developing new field in recent years. Its basic principle is to transport DNA, RNA, antisense oligonucleotide, DNA or RNA editing enzyme to the brain of PD patients by using adeno-associated virus or other vectors to realize the normal expression of genes. By regulating the expression of related genes, the level of essential enzymes involved in dopamine synthesis can be improved, and then the content of dopamine can be restored. Gene therapy can also provide enhanced neurotrophic support to improve the survival rate of DA neurons.[11]

Pathogenesis

Oxidative stress

Reactive oxygen species (ROS) are compounds having oxygen in their molecular composition and particularly active chemical characteristics, and they are a major pathogenic factor in Parkinson's disease.[11]

Mitochondrial dysfunction

Mitochondria is the main place for cell energy supply, which is intimately linked to a number of physiological processes.

Inflammation

Inflammation related to PD includes neuroinflammation and intestinal inflammation. Neuroinflammation is an immune response that plays an important role in protecting neurons, but it may also cause damage to neurons and promote the development of neurodegenerative diseases.[11]

Future Perspectives

The overarching goal of research in PD remains the discovery of disease-modifying and curative options. Until such therapies are clinically available, the focus will continue to be on options for managing the motor symptoms of PD without worsening or causing levodopa-induced fluctuations, as well as reducing disability associated with symptoms that are either less responsive or resistant to levodopa, such as gait and balance, and tremor.[9]

Thus, there remains an ongoing role for investigating non-dopaminergic targets. Basic science research has continued to report that the pathophysiology of levodopa-induced motor fluctuations and dyskinesia involves abnormal pulsatile dopamine receptor stimulation with many post-synaptic non-dopaminergic neurotransmitters and neuromodulatory changes, particularly affecting glutamate, serotonin, and adenosine.[9]

A lack of clinically available drugs that can target non-dopaminergic receptors implicated from preclinical work is a major factor that can limit translational studies.[9]

Another area that may influence development of new non dopaminergic therapies for PD motor symptoms is increased understanding of the heterogeneity of PD. Variability exists in PD subjects in many disease factors, including clinical motor phenotype, such as tremor-dominant versus akinetic rigid types; motor versus non-motor predominance; genetic subtypes; age of onset; pharmacogenomics affecting drug metabolism, among many examples.[9]

REVIEW OF LITERATURE

1. Radhakrishnan and Goyal et al (2018)- Parkinson's disease: A review

Parkinson’s disease is one of the most common neurodegenerative diseases affecting the aging population and is associated with an increased morbidity and mortality. Awareness of the disease manifestations, the treatments, and the progressive long-term course of the disease is necessary for the optimal management of the cases.[12]

2. Thomas B Stoker et al (2020)- Recent developments in the treatment of Parkinson's Disease.

A wide variety of experimental treatment approaches for PD have progressed towards the clinic over recent years. Many previous putative treatments have fallen by the wayside when taken to clinical trials, despite being backed up by promising pre-clinical results, emphasising the need for robust trial design. A greater understanding of the pathogenic mechanisms and anatomical basis for PD symptoms has opened up avenues for new treatment modalities, and it now seems probable that the management of PD will evolve significantly over the coming years.[11]

3. Lalit Kumar et al (2024)- Comprehensive Review on Parkinson's Disease: Insights into Prevalence, Pathophysiology, Diagnosis, and Multifaceted Treatment Approaches.

This review covers Parkinson's disease, emphasizing its growing prevalence, complex pathophysiology, challenging diagnosis, and diverse treatment approaches. Despite diagnostic challenges, recent criteria improvements aim to enhance accuracy, particularly in detecting prodromal stages.[3]

4. Charles L. Mitchell et al (2024)- Novel strategies in Parkinson’s disease treatment: a review

Over the past decade, major progress in the understanding of the underlying molecular cause of PD was made. Microscopic analysis of LBs, intracellular formations observed in midbrain, hypothalamus and thalamus of PD patients.[4]

5. Bastiaan R. Bloema et al (2023)- The Etiology of Parkinson’s Disease: New Perspectives from Gene-Environment Interactions

While elucidation of the involved genetic factors can provide essential insights into the involved pathophysiological processes, identification of responsible environmental factors (many of which appear to be man-made) is paramount from a perspective of prevention. Such prevention measures will become essential if we want to stop the rapid growth of PD worldwide.[5]

6. Nikita Saraswat et al (2023) - A detailed review of pathophysiology, epidemiology, cellular and molecular pathways involved in the development and prognosis of Parkinson’s disease with insights into screening models.

Parkinson's disease is a progressive neurodegenerative disease condition that develops both motor and non-motor symptoms. The motor signs like tremors, resting, bradykinesia, and stiffness which have been determined to be striatal dopamine deficiency and nonmotor symptoms include disorders of sleep, sadness, and cognitive abnormalities.[6]

7. TomasBj¨ orklund et al (2021)- Next-Generation Gene Therapy for Parkinson's Disease Using Engineered Viral Vectors

We expect that we will see some of the herein presented capsids moving to 320 the clinic for multiple indications, not least PD. While a challenging road ahead, the future is bright for gene therapy, and we will see many more capsids emerging with even greater potential.[7]

8. Jinting He et al (2024)- Emerging perspectives on precision therapy for Parkinson's disease: multidimensional evidence leading to a new breakthrough in personalized medicine

The extensive work of PD genome-wide association studies (PD GWAS) has identified an increasing number of loci associated with an increased risk of the disease. By integrating expression, epigenetic, and genomic association studies, candidate genes for PD are identified.[8]

9. Jie Tong et al (2024)- The pathogenesis and treatment of Parkinson's disease

New treatments like gene therapy and cell replacement therapy can cure PD at its root cause, however, issues like immunological rejection and ethics must be taken into consideration. It is hoped that with the continuous development of life science and technology, researchers can further clarify the pathogenesis of PD and propose more effective treatment methods so that human beings can better cope with PD in a society with an aging population and rising incidence.[11]

10. Sara Pisani, MSc et al (2022)- Neuroanatomical substrates in Parkinson's Disease psychosis and their association with serotonergic receptor gene expression: A coordinate-based meta- regression analysis

In there was grey matter volume loss in the parietal-temporal-occipital region which persisted even after adjusting for the effects of PD medications and cognitive scores. Although it may be premature to infer definite conclusions, the above evidence suggests that anomalies in brain regions involved in processing visual stimuli, over reliance and integrating endogenous and externally derived information may underlie psychosis in PD.[12]

AIM AND OBJECTIVE

AIM-Review on Parkinson's disease – Etiology, pathophysiology and Emerging therapies.

OBJECTIVES

1. To provide an overview of the current understanding of Parkinson's disease aetiology, pathophysiology, and clinical features.
2. To examine the genetic and environmental factors contributing to Parkinson's disease development.
3. To explore emerging therapies, including gene therapy, stem cell therapy, and immunotherapy.
4. To review the clinical presentation and progression of Parkinson's disease, including motor and non-motor symptoms.

PLAN OF WORK

1. Literature survey
2. Understand pathophysiology of Parkinson’s disease
3. Emerging therapies
4. Management of Parkinson’s disease.

CONCLUSION

Parkinson's Disease is a complex and multifactorial neurodegenerative disorder characterized by dopaminergic neuron degeneration, alpha-synuclein aggregation, and neurotransmitter imbalance. The pathophysiology of PD involves a intricate interplay between genetic, environmental, and molecular mechanisms**.**

This review highlights the complexities of Parkinson’s disease and the progress made in understanding it’s aetiology and pathophysiology. Emerging therapies offer hope for improving patients outcomes, and ongoing research aims to address the unmet needs of this devastating disease.

REFFERANCE

1. Lalit Kumar *1(2024) Comprehensive Review on Parkinson's Disease: Insights into Prevalence, Pathophysiology, Diagnosis, and Multifaceted Treatment Approaches.
2. Paulina González-Latapi et al(2020) Non-Dopaminergic Treatments for Motor Control in Parkinson's Disease: An Update. Northwestern University.

3. Cassidy Vella1, Renald Blundell1, 2(2024) A review on the nutraceuticals of Parkinson's disease: Department of Physiology and Biochemistry, Faculty of Medicine and Surgery, University of Malta, Imsida MSD2080, Malta.
4. Charles L. Mitchell 1,2 and Dmitry Kurouski (2024) Novel strategies in Parkinson's disease treatment: a review 1Interdisciplinary Program in Genetics and Genomics, Texas A&M University, College Station, TX, United States.
5. Bastiaan R. Bloema,∗ Jolien S. Bogersa and Jonas M. Den Heijer(2023) The Etiology of Parkinson's Disease: New Perspectives from Gene-Environment Interactions.
6. Ayesha Sayyaed1, Nikita Saraswat1*, Neeraj Vyawahare1 and Ashish Kulkarni(2023) A detailed review of pathophysiology, epidemiology, cellular and molecular pathways involved in the development and prognosis of Parkinson's disease with insights into screening models.
7. TomasBj¨ orklund∗ and Marcus Davidsson Next-Generation Gene Therapy for Parkinson's Disease Using Engineered Viral Vectors.
8. Jinting He et al (2024):- Emerging perspectives on precision therapy for Parkinson's disease: multidimensional evidence leading to a new breakthrough in personalized medicine.
9. Paulina González-Latapi Northwestern University :- Non-Dopaminergic Treatments for Motor Control in Parkinson's Disease: An Update.
10. Nataša Klepac1 Mario Habek1 ivan Adamec1 Anabella Karla Barušić1 ivo Bach1 Eduard Margetić2 Ivo Lušić3: An update on the management of young-onset Parkinson's disease.
11. Jie Tong: The pathogenesis and treatment of Parkinson's disease :Second Clinical School, Huazhong University of Science and Technology Proceedings of the Climate Change and Emerging Health Threats: Navigating the Future of Public Health - ICEGEE 2024 DOI: 10.54254/2753-8818/47/2024PJ0101
12. Sara Pisani, MSc, 1, Brandon Gunasekera, MSc: Neuroanatomical substrates in Parkinson's Disease psychosis and their association with serotonergic receptor gene expression: A coordinate-based meta- regression analysis.
13. Divya M Radhakrishnan, Vinay Goyal: Parkinson's disease: A review.