A review on Parkinson's disease

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Fig. 1 Parkinson's disease

Abstract- **In neurological practice, Parkinson's disease is a prevalent movement illness that can be difficult to diagnose and treat. Considering that PD patients have a wide range of motor and non-motor symptoms, the diagnosis is clinical and occasionally challenging. Parkinson's disease (PD) is a progressive neurodegenerative condition primarily brought on by a brain dopamine deficiency. Dopaminergic cell death causes a reduction in dopamine levels in Parkinson's disease (PD) brain tissue. Dopamine is a neurotransmitter involved in motivation, movement, memory, and other processes. In the brains of PD patients, dopamine depletion contributes to motor inadequacy and may also be the source of the cognitive impairment seen in certain PD patients. The hallmark motor symptoms of Parkinson's disease include bradykinesia (slowness of movement), resting tremors, rigidity, and postural instability. These symptoms can significantly impair a person's ability to perform daily activities and lead to a decreased quality of life. Non-motor symptoms, such as depression, anxiety, cognitive impairment, and autonomic dysfunction, are also common and can further complicate the management of the disease. Diagnosis of Parkinson's disease is primarily based on clinical assessment and the presence of characteristic motor symptoms. There are no definitive laboratory tests to confirm the disease, although neuroimaging techniques such as MRI and DaTscan can help rule out other conditions with similar symptoms.**

Key words- **Neurodegenerative disorder, Movement disorder, Dopaminergic medication, Deep brain stimulation, Levodopa.**

INTRODUCTION

Parkinson's disease (PD) is a chronic, progressive neurodegenerative disease characterized by motor and nonmotor symptoms. Its main cause is PD, but secondary causes include diseases mimicking PD and drug-induced causes. Symptoms include resting tremor, bradykinesia, and muscular rigidity. PD significantly impacts patients, families, and caregivers[2]

Parkinson's disease (PD)is a long-term, progressive neurodegenerative condition marked by the widespread presence of the intracellular protein alpha synuclein (aSyn) and the early, significant loss of dopaminergic neurons in the substantia nigra pars compacta (SNpc). Classic Parkinsonian motor symptoms, such as bradykinesia, tremor, stiffness, and later postural instability, are caused by a dopamine shortage in the basal ganglia. Non-motor symptoms, which may appear more than ten years before motor symptoms, are also linked to Parkinson's disease. In the latter stages of Parkinson's disease, these non-motor symptoms start to cause problems. Pharmacological treatment is still the cornerstone of PD care; nevertheless, in advanced illness, these symptomatic medications have significant limits.[3]The hallmarks of Parkinson's disease (PD) include stiffness, postural instability, bradykinesia, rest tremor, and a host of other motor and non-motor symptoms.1-3 The scientific community is paying more attention to age-related disorders like Parkinson's disease as the world's population ages and lives longer. Today, neurological illnesses account for the majority of disabilities worldwide, with Parkinson's disease (PD) having the quickest rate of growth [1]Research suggests that Parkinson's disease

pathophysiological changes may begin before motor symptoms and include non-motor symptoms like restlessness, wretchedness, and subjective changes. Current treatments aim to improve side effects, but further research is being conducted on preliminary neuroprotective medications to potentially moderate or counteract the progression of symptoms.[4]

Pathophysiology-

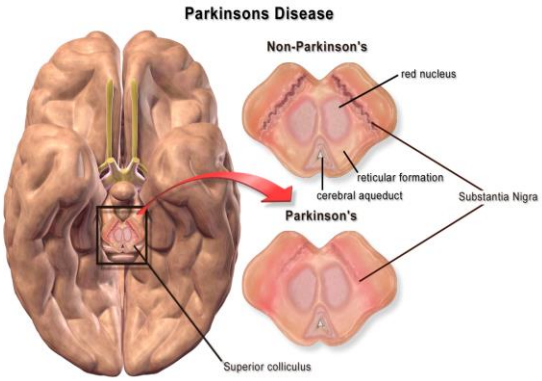

Fig.2.pathophysiology of parkinsons disease

Parkinson's disease is a motor disorder affecting the extrapyramidal framework, affecting motor structures in the basal ganglia. It results in a loss of dopaminergic capacity and decreased motor work, with dopamine in the nigrostriatal tracts and acetylcholine expanding. The disease is believed to cause a 70% to 80% loss of nigral neurons.[4] Pathophysiologically described as dopaminergic neuronal loss or degradation in the SN, Lewy body (LB) is a pathologic feature of dopaminergic neurons that is improved in Parkinson's disease (PD). It could take several years to show any symptoms of a pathologic alteration. The absence of dopamine-producing neurons severely compromises motor function. Numerous proteins, such as ubiquitin alpha-synuclein and ubiquitin, are present in LB aggregation and impede optimal neuron function. According to recent recommendations, neuropathology is a result of both aging and environmental stress. A persistent low-stage mental illness called "inflammation" is brought on by environmental contamination (such as pesticides), the strain of aging, or medication abuse. This inflammatory process is the reason behind the gradual cellular aging of brain neurons.[5]The distribution of lewy bodies serves as the foundation for his pathological staging.PD's pathological hallmark is a lewy body. These are synuclein-immunoreactive inclusions composed of several neuro-filament proteins and proteolysis-related proteins.Among them is the heat shock protein ubiquitin, which is crucial in directing the degradation of other proteins. Lewy bodies are also observed in certain familial forms of Parkinson's disease (PD) caused by mutations in the a-synuclein gene. In juvenile cases, mutations in the parkin protein result in a parkinsonian syndrome without lewy bodies, indicating that the parkin protein is crucial for the formation of the lewy body. Research has demonstrated that parkin promotes ubiquitin's binding (ubiquination) to other proteins, including the a-synuclein interacting protein synphilin-1, which results in the development of lewybodies[6]The pathophysiology of Parkinson's disease extends beyond the dopaminergic nigrostriatal pathway. It is easier to understand non-motor symptoms when considering the consequences of multi-system neurodegeneration. Research over many years indicates changed cholinergic neurotransmissions. The nucleus basalis of Meynert, which supplies the cerebral cortex's cholinergic innervation, contains neurons that contain LBs Dementia, despair, and apathy are among the symptoms of Parkinson's disease (PD) caused by the degeneration of the basal forebrain complex, which supplies the primary cholinergic input for the entire cortical mantle PD frequently causes anosmia and hyposmia as side effects. Although the exact etiology is unknown, α-synuclein deposits in the limbic rhinencephalon, medulla oblongata, anterior olfactory nucleus, and olfactory bulb may be linked to it. There is also progressive, non-linear loss of serotonergic terminals.[7]

Epidemiology-

As one ages, both the incidence and prevalence of Parkinson's disease (PD) rise, impacting 1% of those over 65.(Source:) The emergence of parkinsonian characteristics prior to the age of 40 is known as early-onset Parkinson's disease (EOPD). About 3–5% of all PD cases are related to it. It falls into two categories: "young-onset" PD (YOPD, occurring in the age range of 21–40 years) and "juvenile" PD (occurring before the age of 21).[/2] In most groups, men are twice as likely as women to get Parkinson's disease.[3–4]. There is evidence that female sex hormones have a protective impact. This male prevalence may be explained by the existence of gender-associated

genetic processes or/and gender-specific differences in exposure to environmental risk factors.[3]

Causes-
Genetic PD-Wilson's disease is an autosomal recessive disorder characterized by hepato-lenticular degeneration and copper buildup due to a mutation in the ATP7B gene. linked to liver disease, chorea, dystonia, "wing-beating" tremor, and neuropsychiatric disorder. Up to 95% of patients have Kayser-Fleischer rings visible on slit-lamp examination .Low serum caeruloplasmin, low serum and high Parkinsonism's extrapyramidal characteristics can also appear in neurodegeneration associated with brain iron accumulation (NBIA) syndromes, Huntington's, Fragile X-associated tremor/ataxia syndrome (FXTAS), and the autosomal dominant spinocerebellar ataxias (SCAs).[8]

Envirnmental factors-Over the course of the last 20 years, researchers have discovered more than a dozen environmental factors that are linked to an increased risk of Parkinson's disease (PD), and for the most part, these findings hold true across many studies.Examples include positive associations with traumatic brain injury use of specific pesticides and ibuprofen use as well as inverse associations with smoking coffee consumption intense exercise and plasma urate Biological theories that make sense have been put out for the majority of these relationships. It has been exceedingly challenging to draw a causal conclusion from these epidemiological findings, nevertheless. Reverse causation—that Parkinson's disease develops before a clinical diagnosis alters lifestyle and behavior rather than the other way around—is a reasonable prospective explanation for the majority of these epidemiological results, aside from the sparse andfrequently conflicting experimental data.[9]PD incidence may be related to chemical exposure at work, according to certain research Numerous professions, some of which carry a higher risk, have been studied, including agriculture, pesticide use and heavy metal handling We have also looked at other null effect occupations, like electrical work, working with very low frequency magnetic fields diesel vehicle pollutants, and solvents .[10] A study involving twins found that those who had occupational exposure to TCE had 500% increased risk of developing PD compared with their unexposed twin. Moreover, TCE when fed to laboratory animals also reproduced key features of the disease.[11]

Oxidative stress-The primary cause of Parkinson's disease (PD) is the death of dopamine-producing neurons in the nigrostriatal pathway.6, 8 Unstable free radicals contributing to nerve cell damage is one idea for the cause of Parkinson's disease (PD) that is receiving more consideration. The body's regular chemical reactions produce oxidative stress, which results in the radicals.[12]

1) *Other causes of parkinsonism-.Medication (also known as "drug-induced Parkinsonism"):* A condition in which symptoms appear after taking specific drugs, such as some antipsychotic drugs, and typically go away when the drug is stopped.[13]
2) *other progressive brain condition*- progressive brain disorders include corticobasal degeneration, multiple systems atrophy, and progressive supranuclear palsy.[13]
3) *cerebral infraction* -A cerebral infarction occurs when a severe stroke results in the death of multiple brain regions.[13]

- *Signs and symptoms-*

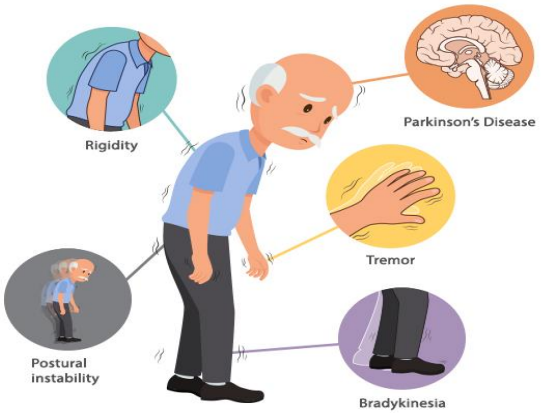

Fig.3 sign and symptoms of parkinsons disease.
signs and symptoms of Parkinsons divided into two categories :

- *Motor symptoms* -Symptoms that impair bodily movement are referred to as motor symptoms. These are Parkinson's disease's most blatant signs. Parkinson's disease (PD) is primarily characterized by tremor, bradykinesia, stiffness or rigidity, and poor balance or postural instability. In the early

stages of the illness, these symptoms are typically not too severe.[14]

1) *Tremor* -When the afflicted body part is at rest, tremors (shaking) brought on by Parkinson's disease are most apparent. Early PD is characterized by an intermittent tremor that may go unnoticed by others; some patients describe an imperceptible "internal shakiness" in their limbs or body. When the tremor manifests itself, it usually affects one hand and is referred to as "pill-rolling." Over a few years, the tremor typically moves to the opposite side of the body. Stress, excitement, and anxiety can make the tremor worse. The tremor may also affect other body parts, such as the tongue, lips, jaw, or legs. Still, the head is usually unaffected by Parkinson's disease tremor.[14]A generalized slowness of movement is known as bradykinesia. Everyone with Parkinson's disease eventually experiences it, and it can cause fatigue, weakness, or incoordination.
2) *Bradykinesia*-Bradykinesia in the arms can make it difficult to perform activities like typing, buttoning clothing, tying shoelaces, double-clicking a computer mouse, and retrieving coins from a pocket or purse. Bradykinesia can make a person feel unsteady, drag their legs when walking, or take shorter, shuffling steps. Additionally, a person might find it difficult to get out of a car or stand up from a chair.[14]
3) *Rigidity*-Rigidity makes it difficult for the arms, legs, or body to move freely. It typically starts on the same side of the body as bradykinesia and tremor, two other early symptoms.[14]
4) *Poor balance (postural instability):* When we stand or walk, our brains' automatic reflexes help us maintain our balance. These reflexes malfunction in PD patients, which makes them prone to falling or feeling unsteady. Postural instability, or losing one's balance and falling.[14]

- *Non motor symptoms*-Constipation, rapid eye movement (REM) sleep behavior disorder (RBD), anosmia, anxiety, depression, and other non-motor symptoms (NMS) can occur a decade or two before motor symptoms. Particularly in the early clinical trials that focused primarily on controlling motor features, they were largely eclipsed by motor features. Grading scales have been developed and integrated into clinical trials as a result of the recognition of NMS as a significant cause of concern for patients over the past twenty years or so.Later stages of PD are often accompanied by hallucinations. They begin with images that are amiable and non-threatening, then they turn scary. If the hallucinations don't pose a threat, there is no need for treatment. The first step in treating patients or caregiverswho express a need for treatment is to stop using drugs that have a higher potential for hallucinations and less motor benefit.[15]

Diagnosis-

Fig.4 Diagnosis of parkinsons disease.

Identifying the common presenting features of Parkinson's disease (PD) is the first step towards recognizing it.One of Parkinson's disease's problems is that its indications and symptoms are frequently subtle.Unless doctors are actively looking for these symptoms and signs, they may only consider a diagnosis of Parkinson's disease (PD) when more notable findings are made. The majority of family physicians are familiar with the acronym TRAP.[19]According to the clinical diagnostic criteria for Parkinson disease, a person must exhibit parkinsonism, which is bradykinesia accompanied by rigidity, rest tremor, or both19 (Table 2). Individuals must also fulfill at least two of the four supportive criteria for clinically established Parkinson disease (i.e., certainty based on clinical presentation but not pathologic confirmation): Resting tremor, a significant improvement with dopaminergic therapy (e.g., carbidopalevodopa), dyskinesias brought on by levodopa, or both olfactory loss and cardiac sympathetic denervation on iodine-123-meta-iodobenzylguanidine myocardial scintigraphy (an imaging test that evaluates cardiac norepinephrine uptake, which depends on intact postganglionic sympathetic neuron function.[16]

In clinical practice, the diagnosis is usually made on the basis of response to levodopa, associated and exclusionary symptoms, and the presence of a combination of cardinal motor features. Early in the

course of the disease, when signs and symptoms overlap with other syndromes, it can be difficult to distinguish Parkinson's disease (PD) from other forms of parkinsonism, even though the diagnosis is simple when patients present classically.[17]Thereare several other clinical indicators that are noteworthy. Reduced facial expression and a change in handwriting with micrographia are frequently early features. One side's loss of arm swing is another early and helpful diagnostic indicator. It doesn't appear that a glabellar tap is very sensitive or specific.Asking about a diminished sense of smell is still important though, as this could be one of the initial signs of early Parkinson's disease.ThirteenHypophonia, salivary drooling (from decreased swallowing), and impairment of postural reflexes may develop as the disease progresses.[18]

Management –

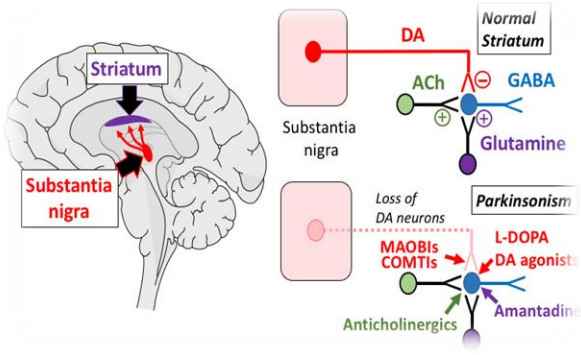

Fig.5 management of parkinsons disease

Dopaminergic therapy-Dopaminergic medications are commonly used to treat motor symptoms in Parkinson's disease (PD), with L-DOPA being the most potent anti-parkinsonian drug. This is because the lack of dopamine in the nigrostratial pathway is the root of many PD symptoms, particularly movement-based ones. L-DOPA is metabolized in the small intestine and converted to dopamine by AADC and COMT, which can be stored in nigrostratial terminals. However, dopamine agonists act directly on postsynaptic receptors, reducing dopamine production.[20]

Anticholinergic therapy: Trihexyphenidyl and benztropine are examples of anticholinergics that block acetylcholine's actions at muscarinic receptors postsynaptic to striatal interneurons. They don't affect bradykinesia and are mostly used to lessen tremor. A number of negative symptoms, including cognitive decline, disorientation, hallucinations, impaired vision, dry mouth, constipation, and urine retention, can be linked to cholinergic antagonistism. Anticholinergics' efficacy in treating Parkinson's disease (PD) is limited by these adverse effects.[21]

Monoamine oxidase inhibitors-Selegiline and rasagiline are MAOIs that are commonly used in individuals with mild to moderate Parkinson's disease (PD), but they are also useful in patients with moderately advanced PD who have motor problems linked to levodopa. When given once daily (50–100 mg/day), safinamide, another MAOI, has been shown to decrease daily and morning off times and enhance mean on time without causing bothersome dyskinesia.90 Safinamide is a reversible MAOI that also lowers glutamate release from neurons by blocking intracellular calcium entry, voltage-dependent activated sodium channel, and neuronal dopamine reuptake.[21]

Deep brain stimulation-Deep brain stimulation received approval as a supplemental treatment to lessen motor fluctuations in patients with severe Parkinson disease .Accepted targets for this operation are the subthalamic nucleus and the globus pallidus interna, with comparable adverse effects and motor function benefits.99,98 Lower doses of dopaminergic drugs were necessary for patients receiving subthalamic nucleus stimulation; nonetheless, depression got worse following subthalamic nucleus stimulation and got better after globus pallidus interna stimulation. The majority of centers base their decision to use deep brain stimulation on the type of symptoms the patient has and how likely it is that they will respond to treatment[.23]

Surgical treatment:

1) *Ablative surgery* -Out of the three major surgical procedures, ablative surgery is the oldest and carries the most risk. Surgery options include thalamotomy, subthalamotomy, and pallidotomy[71]. Figure 1 shows the locations of each surgery as well as the damaged routes. The substantia nigra reticulata and internal globus pallidus are hyperactive due to the lack of dopaminergic innervation, which results in excessive inhibitory output[73,74]. The thalamic

movement-related center is disrupted by the inhibitory output, leading to symptoms of hypokinetic Parkinson's disease (PD)[73]. By making a lesion in the internal globus pallidus, thalamus, or subthalamic nucleus to interrupt the hyperactive pathway, either close to the beginning, as in pallidotomies, or farther down the line, as in thalamotomies, ablative surgery attempts to relieve these symptoms.[22]

2) *Occupational therapy*-Occupational therapy helps patients maintain self-care, work, and leisure activities, and adapt to their physical and social environment as their disease progresses. It works alongside physical therapy (PT) to overcome physical limitations, such as walking, manual activities, and self-transfers. OT focuses on enabling meaningful performance and engagement, using strategies like scheduling, planning activities, and adapting the physical environment. Home-based individual OT sessions can lead to self-perceived performance improvement in daily tasks. Both PT and OT aim to help patients maintain their lifestyles and engage meaningfully.[22]

3) *Cognitive behavioral therapy*-CBT is being considered as a potential treatment for a number of PD symptoms, including depression, sleeplessness, and impulse control issues. One limitation of CBT studies is that they are not amenable to double-blinding. To demonstrate efficacy, more research and replication are required[1]. Moreover, CBT has the drawback that therapy focuses on treating a single symptom, as opposed to treating several symptoms as in PT or OT, or improving the whole system as in SP. For instance, CBT for insomnia differs from other forms of CBT in its fundamental approaches; hence, it is a stand-alone treatment that has no effect on other symptoms[22]

CONCLUSION

One of the most prevalent neurodegenerative illnesses affecting the elderly population is Parkinson's disease, which is linked to a higher rate of morbidity and death. For the best possible care of the patients, it is essential to understand the signs and symptoms of the disease, its progressive long-term course, and the available treatments. Understanding the neuropathology of Parkinson's disease (PD) and how it spreads throughout the nervous system has advanced tremendously. All of these therapies are not curative, though. Parkinson's disease (PD) continues to be a progressive illness that, when treatment-resistant motor problems and non-motor symptoms worsen, ultimately results in severe disability. The main unmet needs that need to be addressed by the current and future research efforts are modifying factors that contribute to the disease's progress.

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