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Review On Parkinson's Disease

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Abstract: Affecting 1% of those over 55, Parkinson's disease [PD] is the second most prevalent neurological illness after Alzheimer's disease. Lewy bodies and a gradual loss of dopaminergic neurons in the substantia nigra pars compacta are hallmarks of the underlying neuropathology observed in Parkinson's disease. The Lewy bodies are made up of α-synuclein aggregates. Bradykinesia, muscle rigidity, and resting tremor are among the motor symptoms of Parkinson's disease. Parkinson's disease (PD) patients typically exhibit bradykinesia, rigidity, rest tremor, and stooping posture, among other motor and non-motor symptoms. PD is also linked to autonomic dysfunction (such as orthostatic and

Hyperhidrosis), cognitive impairment (dementia), and neurobehavioral disorders (such as anxiety and sadness).Medical pharmacologic treatments and cutting-edge surgical procedures like deep brain stimulation (DBS) have proliferated in recent decades. The mainstays of Parkinson disease treatment include deep brain stimulation for patients experiencing uncontrollable LDOPA-related motor complications, non-dopaminergic

methods to treat both motor and non-motor symptoms, and medication replacement of striatal dopamine. Lifestyle changes are helping to avoid Parkinson's disease. Yoga and other physical exercises lower the risk of Parkinson's disease.

Index Terms - Bradykinesia, muscle rigidity, cognitive impairment, orthostatic, Parkinson's disease.

I. INTRODUCTION

Tremor, rigidity, and bradykinesia are the hallmarks of Parkinson's disease (PD), a complicated progressive neurological illness. As the condition worsens, some individuals may experience postural instability. Our understanding of Parkinson's disease is still growing, having been initially defined by James Parkinson in 1817 and then further defined by Jean-Martin Charcot. After Alzheimer's disease (AD), Parkinson's disease (PD) is the second most prevalent neurodegenerative illness. (1)With modest frontal cortical atrophy and occasionally ventricular dilatation, the brain in idiopathic Parkinson's disease is often unremarkable on a macroscopic level. Transverse sections of the brainstem show the primary morphological alteration in Parkinson's disease (PD), with nearly all cases exhibiting loss of the darkly pigmented region in the locus coeruleus and substantia nigra pars compacta (SNpc). The death of noradrenergic neurons in the locus coeruleus and dopaminergic (DA) neuromelanin-containing neurons in the SNpc is directly correlated with this loss of pigmentation. (2) Hematoxylin and eosin-stained coronal section at the substantia nigra pars compacta (SNpc) level in a control brain (A and B) and a Parkinson's disease brain (C and D). The dark brown cells in both sections are dopaminergic (DA) neurons that contain neuromelanin. In the PD brain, dopaminergic cell loss is visible in the SNpc. To provide a closer look at the

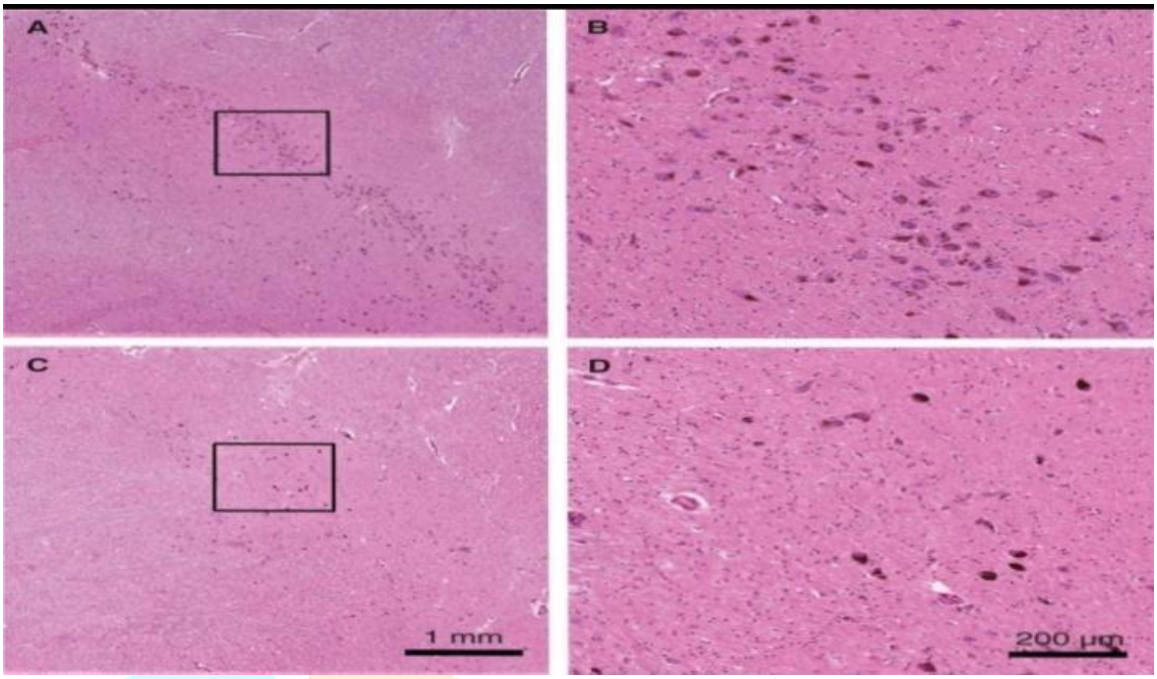


Fig. 1. Parkinson's disease (PD) DA neurons

darker pigmented DA neurons, the squares regions in A and C are magnified in B and D, respectively. Parkinson's disease (PD) is a long-term, progressive neurodegenerative illness marked by widespread intracellular protein alpha synuclein (aSyn) and early, noticeable death of dopaminergic neurons in the substantia pars compacta (SNpc). Bradykinesia, tremor, rigidity, and subsequent postural instability are classical Parkinsonian motor symptoms caused by dopamine deficiency in the basal ganglia. Non-motor symptoms, which may appear more than ten years before motor symptoms, are also linked to Parkinson's disease. As Parkinson's disease progresses, these non-motor symptoms become problematic. Pharmacological therapy is currently the cornerstone of PD care; yet, these symptomatic treatments have significant restrictions in advanced illness. Later in the course of the disease, a number of incapacitating features appear, such as non-motor symptoms, dopamine-resistant motor symptoms, and motor problems from prolonged dopamine therapy. Defined disease-modifying therapy is still missing, despite notable advancements in medical and surgical treatment for Parkinson's disease. Nonetheless, scientists are optimistic that they may be able to pinpoint possible disease modification targets.

EPIDEMIOLOGY

The study of epidemiology Parkinson's disease (PD) affects 1% of adults over 65, and its incidence and prevalence rise with age. (3) Since the early 1800s, when the doctor who gave the disease its name first described it, Parkinson's disease has been understood to exist. PD, sometimes known as "paralysis agitans," is rare in young adults, particularly those under 40. (4) One prevalent and expensive neurological condition is Parkinson's disease (PD). According to a recent estimate, at least one million Americans are impacted, and the annual expenses come to almost $52 billion. The incidence of Parkinson's disease (PD) varies from 5/100,000 to over 35/100,000 new cases annually, according to estimates based on healthcare utilization. (5) Unless more efficient cures, treatments, or preventative measures are found, the societal and financial cost of Parkinson's disease will rise in tandem with this growth. There are notable differences in Parkinson's disease epidemiology by age, sex, location, ethnicity, and period. Globally, prevalence has risen in addition to demog-raphic shifts. The decrease in other competing causes of death is one of numerous possible explanations for this increase. It is less clear whether the incidence is rising, particularly among women or in many low- and middle-income nations where high- quality data is scarce.

Numerous environmental factors, such as exposure to neurotoxic chemicals, have been proposed as explanations for the higher prevalence of Parkinson's disease in men and older adults. Ethnic inequalities in illness risk seem to exist within nations, albeit these variations may be due to disparities in access to medical care.

ETIOLOGY

We now have a far better grasp of the causes of Parkinson's disease than we did a century ago. Loss of pigmentation in the midbrain's substantia nigra was initially identified as a characteristic of post-mortem brain examinations of Parkinson's disease patients in 1919. It was further recognized in the 1950s that the pigmented neurons lost in the substantia nigra are dopaminergic, and that the mechanism of the movement dysfunction in Parkinson's disease is related to the loss of dopamine in subcortical motor circuitry. (6) (7) Since one family member with PD increases the incidence of the disorder in siblings, genes have a significant role. Additionally, these occurrences usually happen considerably earlier in life. There has been discussion on the relative roles of genes and environmental/lifestyle variables in the pathophysiology of MiPD. Age is the primary risk factor for Parkinson's disease (PD), with a median age at onset of 60 years. Both hereditary and environmental factors contribute to Parkinson's disease (PD), which is a complex illness. With a median beginning age of 60, aging is the largest risk factor for Parkinson's disease. (8)

- **Cigarette smoking**: The effects of cigarette smoking on Parkinson's disease have been well investigated, with largely consistent findings. Larger cohort studies concur with the majority of epidemiological reports, which are case-control studies demonstrating a lower chance of developing Parkinson's disease. (9) We still don't fully understand the factors that contribute to this related decreased risk. In animal models of Parkinson's disease, it has been demonstrated that nicotine or selective agonists can neuroprotectively activate the nicotinic acetylcholine receptors on dopaminergic neurons. (10) (11) It is difficult to confirm whether smoking prevents Parkinson's disease (PD) or whether PD helps prevent the habitual use of cigarettes because nicotine can also boost the production of dopamine, which is involved in the disease's subsequent mechanisms. Patients with Parkinson's disease (PD) may be less prone to addictive behaviors and, thus, less likely to smoke due to a decrease in dopamine. The ability of PD and prodromal PD patients to quit smoking far more readily than controls lends credence to this theory, indicating that this link may be caused by a reduced sensitivity to nicotine. (12)
- **Genetic**: Although Parkinson's disease (PD) is typically an idiopathic condition, a small percentage of sufferers (10–15%) record a family history, and roughly 5% have Mendelian inheritance.

Furthermore, as-yet-poorly characterized polygenic risk factors contribute to an individual's risk of Parkinson's disease. In the order that they were discovered, the genes that have been linked to Parkinson's disease are given the "PARK" moniker. 23 PARK genes have been connected to Parkinson's disease thus far. Table 1 lists the PARK gene mutations that exhibit either autosomal dominant (like SCNA, LRRK2, and VPS32) or autosomal recessive inheritance (like PRKN, PINK1, and DJ-1). While some of these genes—PARK5, PARK11, PARK13, PARK18, PARK21, and PARK23—have not been proven to be involved, others—PARK3, PARK10, PARK12, PARK16, and PARK22—are thought to be risk factors. (13)

Table 2 Summary of familial PD mutations that have been replicated in animal models

Locus	Gene	Mutation
PARK1	SNCA	A30P, A53T, E46K
PARK2	PRKN	Various mutations, exonic deletions, d and triplication
PARK4	SNCA	Duplication and triplication
PARK5	UCH-L1	I93M and S18Y
PARK6	PINK1	G309D, exonic deletions

Table 1 lists the PARK-designated genes linked to Parkinson's disease in families.

- **Caffeine:** mostly derived from plants, caffeine 3,7-trimethylpurine-2,6-dione is a psychoactive methylxanthine. Many drinks, including tea and coffee, contain it. (14) In the Fig (3) transgenic AD mouse model, coffee reduced the amyloid load and reversed the cognitive impairment. (15)

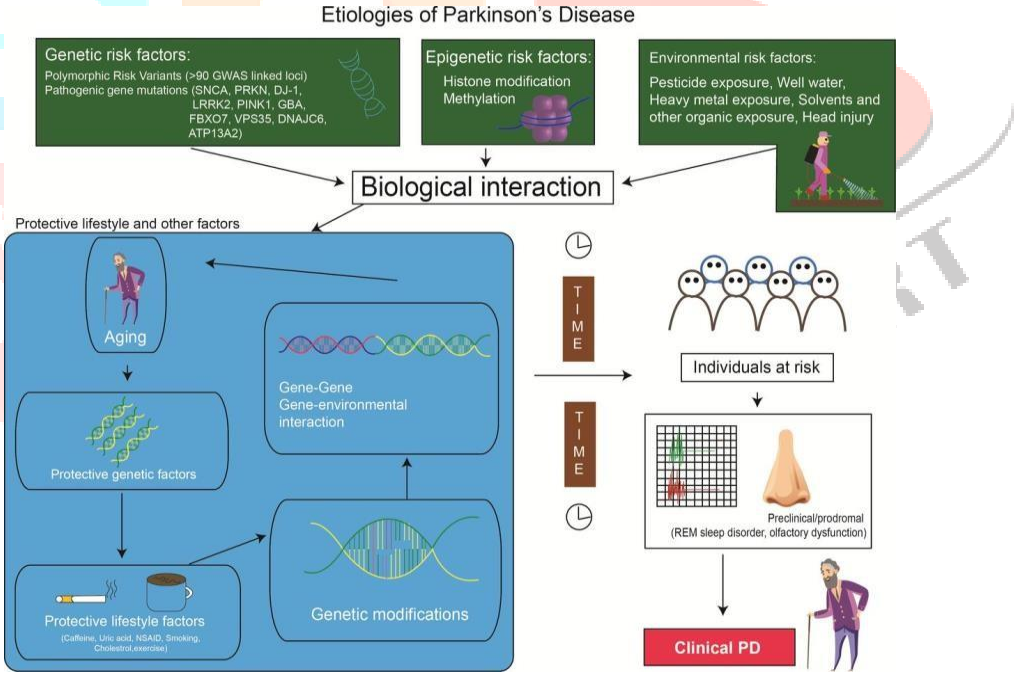


Fig.3. Etiology of Parkinsons Disease

PATHOPHYSIOLOGY:

The formation of Lewy Bodies, a pathologic hallmark in dopaminergic neurons, and loss or degeneration of the dopaminergic (dopamine-producing) neurons in the substantia nigra constitute the pathological definition of Parkinson's disease. (16) Motor control is significantly compromised as a result of this preferential loss of dopamine-producing neurons. Alphasynuclein and ubiquitin are two proteins found in Lewy bodies, or aberrant intracellular aggregates, which hinder proper neuronal function.

. The fictitious brain circuit that causes PD rest tremor to start and spread is depicted in this image. The cerebello-thalamo- cortical circuit (red) generates the tremor amplitude, while the basal ganglia (blue) start a tremor episode, according to the dimer-switch concept At the motor cortex level, these circuits converge. The dopaminergic retrorubral area (which affects the cerebral tremor circuit through the basal ganglia and VLp), the noradrergic locus

coeruleus (which affects the cerebral tremor circuit through the VLp), and the serotonergic raphe nuclei (uns-ure, where this region targets the cerebral tremor circuit) are among the important neurotransmitter systems involved. Although this needs further investigation, distinct activity originating from trembling muscles may merge with brain networks, maybe at the level of the cerebellum and/or thalamus. Green bolts, on the other hand, stand in for targets for non-invasive brain stimulation methods. Only in cases of postural tremor in Parkinson's disease is the cerebellum a target. MC stands for motor cortex; GPe and GPi for globus pallidus externa and interna, respectively; STN for subthalamic nucleus; VLa and VLp for ante-rior and posterior ventrolateral thalamic nuclei; CBLM for cerebellum; LC for locus coeruleus; and RRA for retrorubral area. (The reader is directed to the online version of this article for an interpretation of the color references in this figure legend.)Lewy body (LB), a pathologic feature of dopaminergic neurons, is enhanced in Parkinson's disease (PD), which is characterized as pathological as dopaminergic neuronal loss or degradation in the SN. It could be years before any indication of a pathologic alteration appears. Significant impairment of motor function results from this deficiency in dopamine-producing neurons. Numerous proteins, such as ubiquitin alpha-synuclein and ubiquitin, are present in LB aggregation.(17)

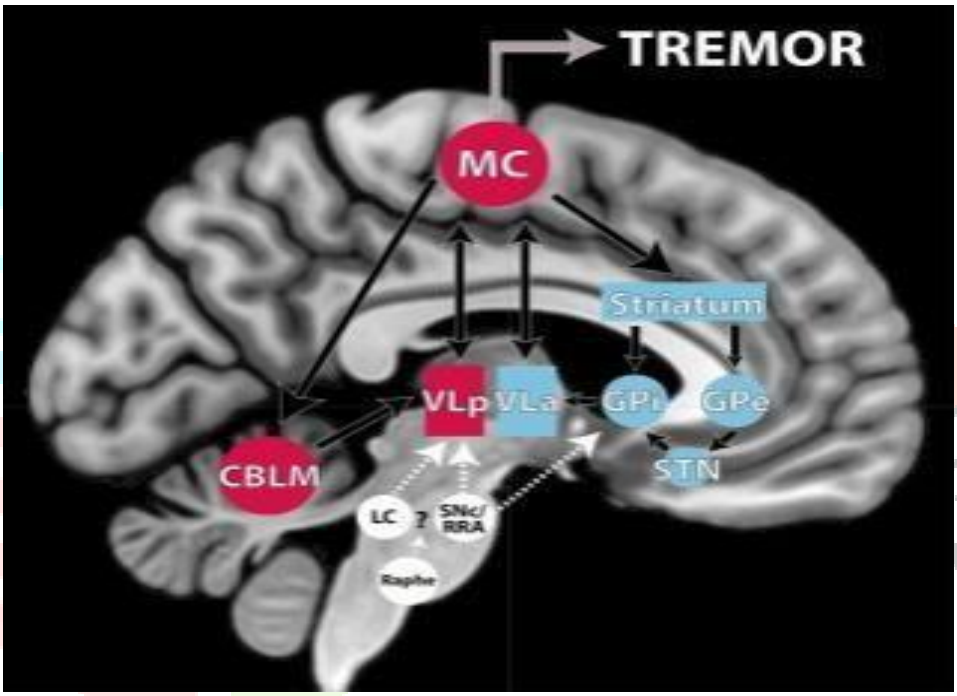


Figure 4: The pathophysiology of Parkinson's disease

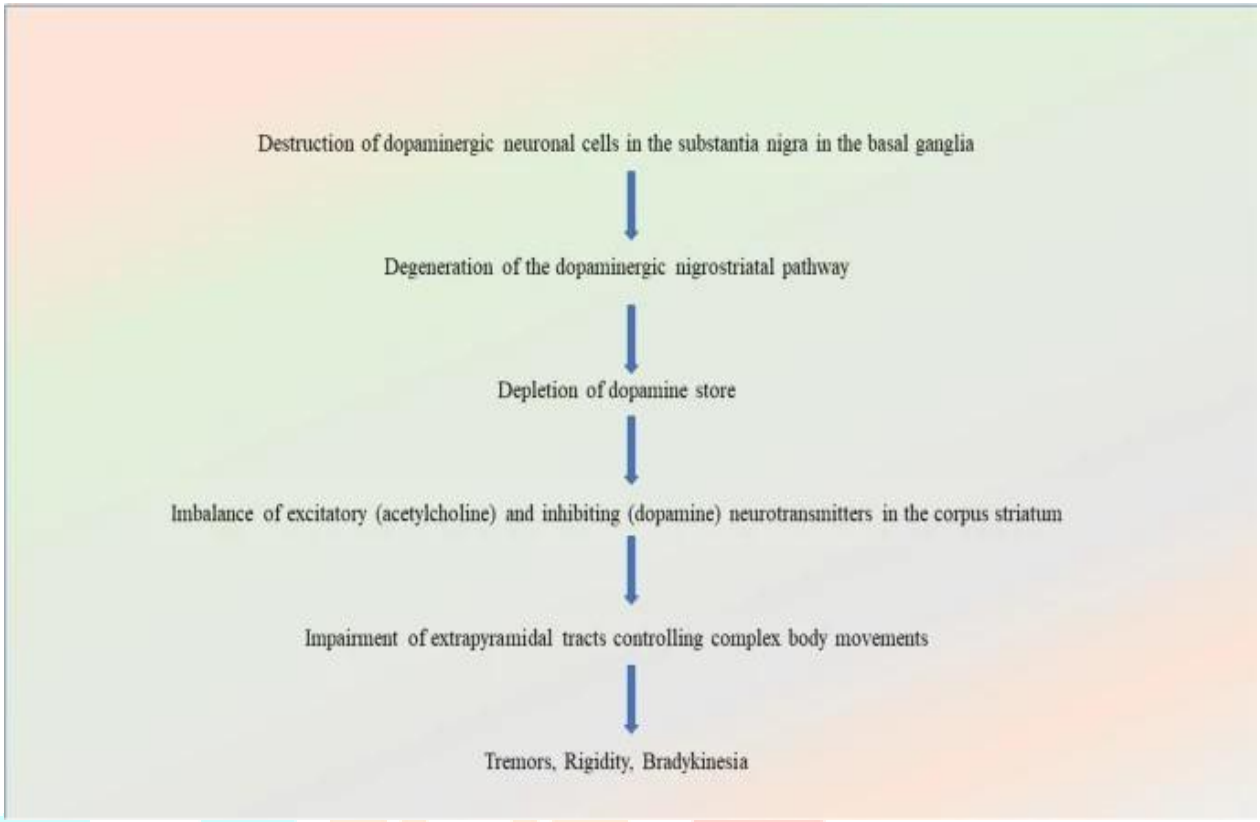


Fig. 5. Destruction of dopaminergic neuronal cell

Induce movement limitations due to a dopaminergic imbalance. K+ channels, however, improve these. Dopamine: The substantia nigra degenerates in Parkinson's disease (PD), disrupting the nigrostriatal pathway. The resulting decrease in striatal dopamine is the neurochemical underpinning of Parkinson's disease. The development of Parkinson's disease motor symptoms appears to be dependent upon and sufficient for the impairment in striatal dopaminergic transmission. Levo-dopa is derived from dopamine. Dopamine does not cross the BBB on its own. Active transport of levodopa into the brain occurs, where it is transformed into dopamine. Drugs decarboxylate dopamine in the brain's periphery. As a result, a high dosage of levodopa is needed. (19) Eighty-three percent of PD patients get dementia after 20 years of the illness. These levodopa-resistant late-stage Parkinson's disease symptoms and signs considerably worsen disability and are trustworthy predictors of death and hospitalization. (20)

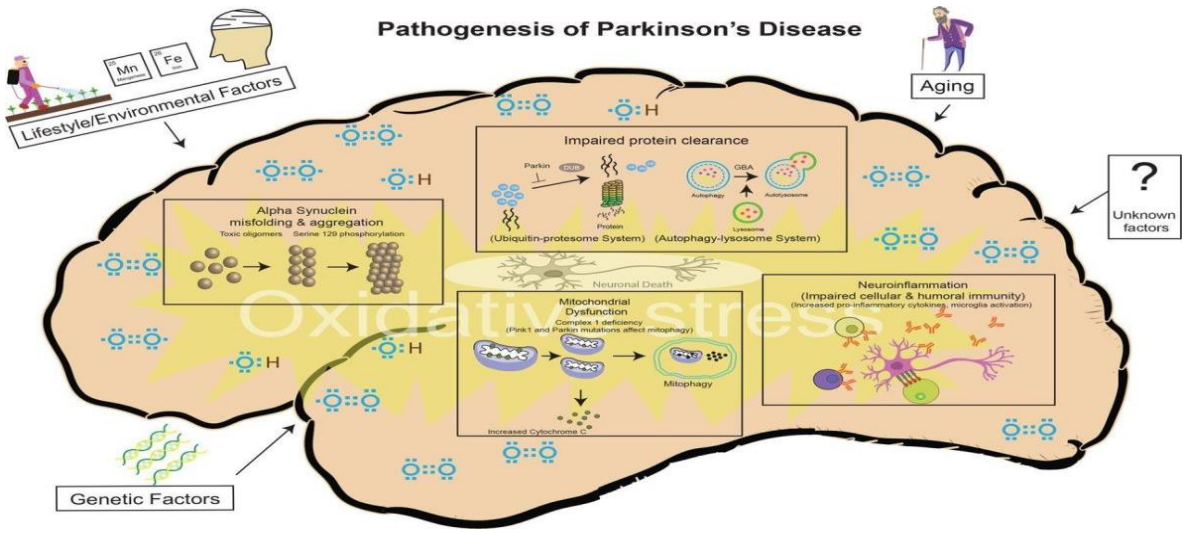


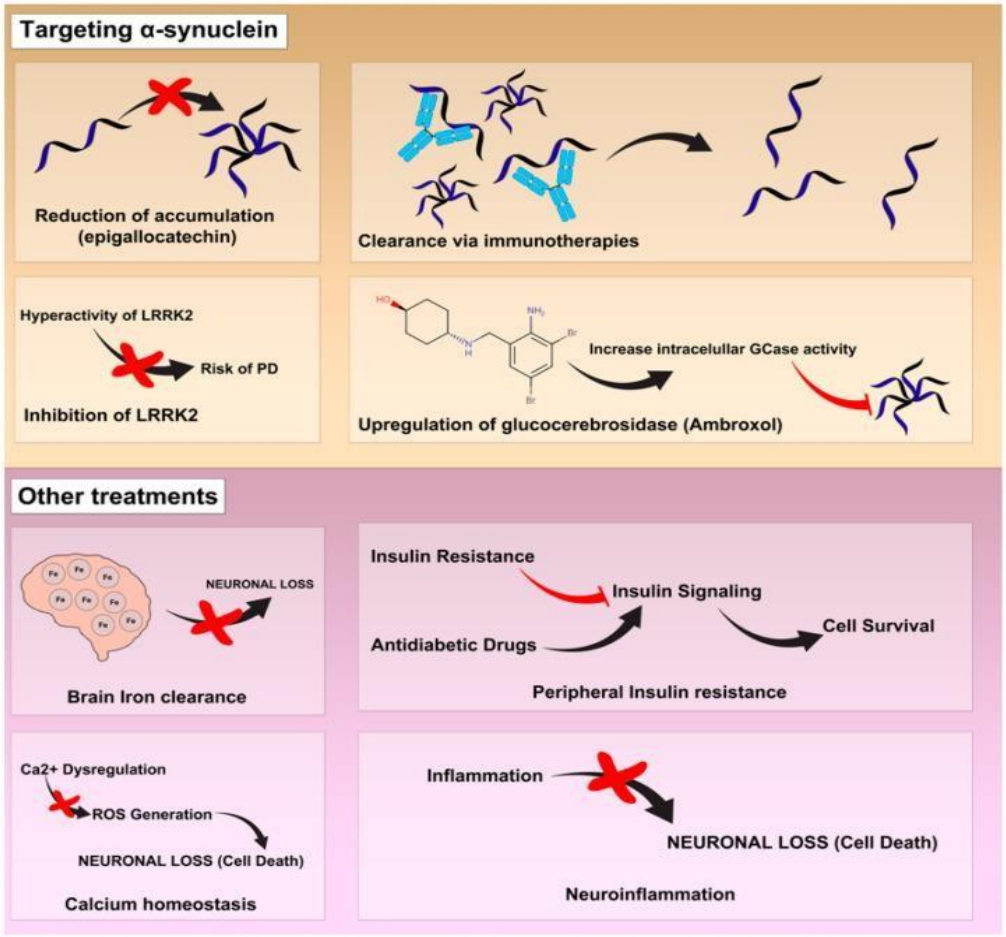
Fig. 6. Pathogenesis of Parkinson's disease

PD genetics Only 5–10% of all cases of Parkinson's disease are genetic. (21) Parkin (PARK2), leucine rich repeat kinase 2 (LRRK2/PARK8), alpha synuclein (SNCA-PARK1/PARK4), PTEN- induced putative kinase 1 (PINK1/PARK6), DJ1 (PARK 7), ubiquitin C-terminal hydrolase like 1 (UCH-L 1), and ATPase type 13A2 (ATP13A2) are the main genes that have been identified and shown to be causative in Parkinson's disease. (22) The substitution of serine for glycine at position 2019 is the most common and thoroughly researched LRRK2 mutation. (23) Early start of AD is caused by a point mutation in the SNCA gene, while overexpression of the gene results in the onset of PD symptoms later in life, in the fourth or fifth decades. (24) (25)

Dopaminergic neurons in the substantia nigra pars compacta (SNpc) are lost or degenerated in Parkinson's disease (PD), and the buildup of Abnormal intracellular aggregates called Lewy bodies contain proteins like alpha-synuclein both ubiquitin and aSyn. Before symptoms appear, between 60 and 70 percent of the neurons in the SNpc are destroyed. (25) 26 (28).

Fig.7. Parkinson disease condition

Fig (8)



People with Parkinson's disease (PD) have impaired motor control due to selective loss of dopaminergic neurons in the striatum. Corticostriatal projections from the main motor cortex, supple-mentary motor region, cingulate motor cortex, and pre-motor cortex make form the motor circuit of Parkinson's disease (PD), which ends on the dendrites of the striatal-medium spiny neurons. The direct pathway is a monosynaptic link between the subst-antia nigra pars reticulata (SNpr) and the medium spiny neurons that express dopamine D1 receptors and GABAergic (gamma amino butyric acid-ergic) neurons in the globus pallidus internus (Gpi).The 'indirect' pathway begins with medium spiny neurons expressing D2 receptors, which project to the globus pallidusexternus (Gpe). The STN then connects to the Gpi as a glutamatergic relay. The striatal dopaminergic tone controls the basal ganglia's GABAergic output activity via these two routes.The D1-mediated direct route activity is decreased, whereas the D2-mediated indirect pathway activity is increased. pathway activity, which raises the basal ganglia output neurons' fring rate (GABA) and over- inhibits the thalamocortical and brain stem areas downstream. (29) (30)

RECOGNIZING PARKINSON'S DISEASE:

Symptoms :-

1)Bradykinesia 2) Shivering 3) Stiffness 4) Deformities of posture 5) Unstable posture 6) Freezing7) Sleep disorders

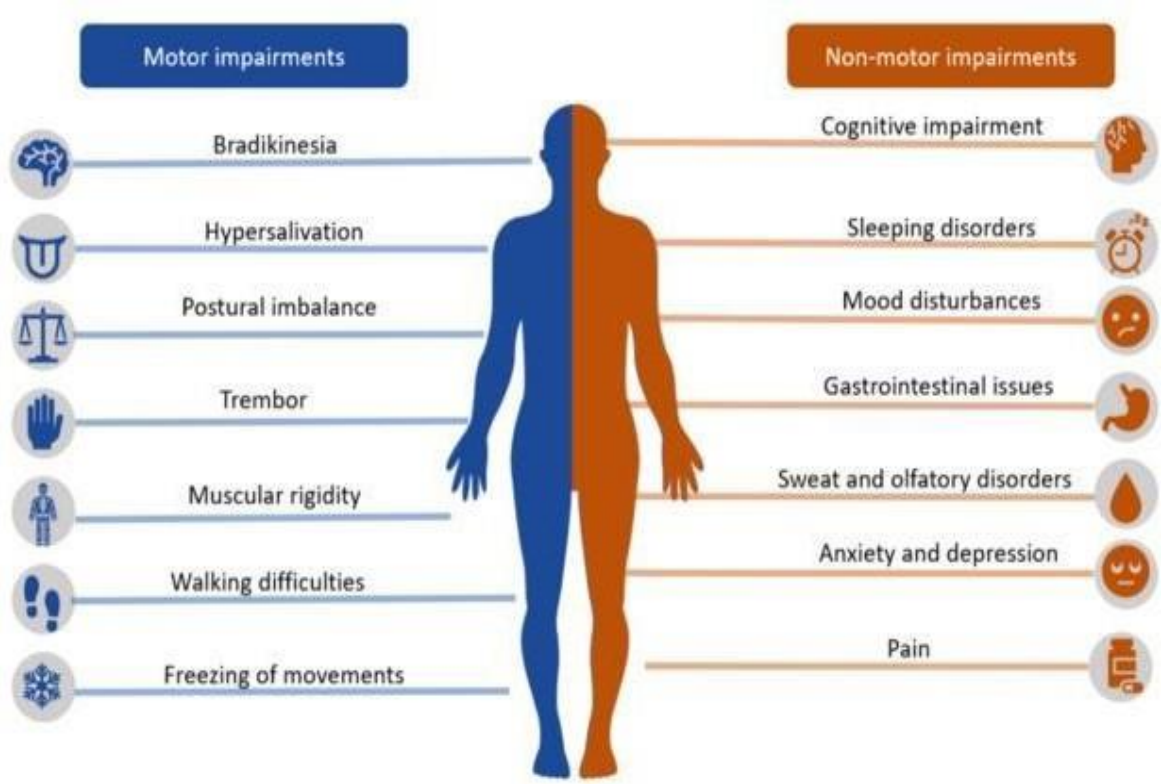
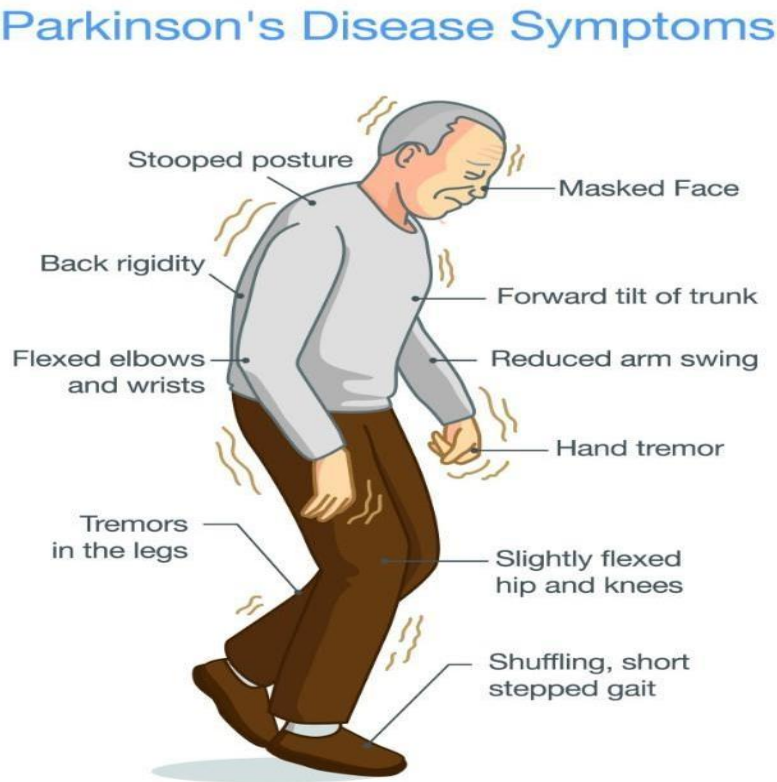


Fig.9. Motor and non - motor impairments

Fig (10)



RISK FACTORS :

1. Tobacco: Numerous prospective studies have found that tobacco smokers had a low risk of developing Parkinson's disease, as have users of smokeless tobacco (such as chewing tobacco) .
2. Traumatic Brain Injury (TBI): According to a 2013 meta-analysis, TBI may be linked to a higher risk of Parkinson's disease (PD) with a risk ratio of about 1.6. (31)
3. Urate: Gout is a natural experiment with conflicting claims of decreased and increased PD risk. At the same time, gout is a natural experiment with conflicting reports of lessened. (32) (33)
4. Age: Despite being considered an old age disease, a small percentage of patients (approximately 5% of all cases) exhibit symptoms before the age of 60. Most of these cases are brought on by mutations in an ever-increasing list of genes that affect either protein metabolism or mitochondrial function, such as alpha-synuclein (PARK 1), DJ-1 (PARK7), Pink1 (PARK6), and Parkinson (PARK 2). This shows that dysfunction in either is sufficient to cause Parkinson's disease. (34)
5. Gender: Men and women have distinct processes that mediate the adaptive mechanisms of dopaminergic neurons that have survived a lesion. In a neurotypical brain, women have higher levels of the genes that are in charge of formaturation and neuronal signal transmission, while men have higher levels of the genes involved in the pathophysiology of Parkinson's disease (PD), such as PINK-1 and α-synuclein. Males are more likely to acquire Parkinson's disease (PD) due to a particular relationship between gender and the gene expression patterns of normal dopaminergic neurons. (35)

TREATMENTS:

Patients, the majority of whom suffer from disabilities brought on by the numerous problems that arise during the course of the disease, have unmet therapeutic needs when there is no treatment available to halt or prevent the advancement of PD. Thus, one of the main challenges facing current research is the hunt for a viable treatment. (36) Dopamine moves on to its metabolism after fulfilling its purpose. Dopamine is metabolized by two enzymes: monoamine oxidase (MAO) and catechol-O-methyl transferase (COMT). Because they exhibit the MAO-B isoform, astrocytes contribute to dopamine metabolism, whereas catecholaminergic neurons express the MAO-A isoform. The majority of COMT expression occurs in glial cells. MAO production falls in the brain when dopamine levels are low. Currently, pharmacological targets of the dopamine metabolism and/or dopaminergic system are being investigated for the treatment of Parkinson's disease. (37) (38) In the meantime, β-adrenergic modulation was proposed as a potential therapeutic strategy to target α-synuclein after an elevated risk of Parkinson's disease was shown after the administration of β-antagonists such propranolol. (39) When levodopa-induced side effects become very bothersome, deep brain stimulation (DBS), another well-established treatment for Parkinson's disease, can be helpful in treating dopamine-dependent motor symptoms. DBS is the surgical placement of electrodes that activate subcortical areas, such as the globus pallidus internus and subthalamic nucleus. (40) (41) Dopamine agonists are linked to a higher overall risk of adverse events, while MAO-B inhibitors are linked to less robust symptom alleviation but a reduced risk of dyskinesia. 45 In the end, the majority of Parkinson disease patients use medications from several classes to achieve complimentary effects while avoiding high dosages and dose-related side effects. (42) Weaning off potentially helpful drugs including anticholinergics, amantadine, dopamine agonists, MAo-B inhibitors, and occasionally levodopa should be the first step in treating psychosis in Parkinson disease. Sometimes the difficult reemergence of previously managed Parkinson disease symptoms limits weaning. Three primary alternatives are available if psychosis continues and needs to be treated: quetiapine, clozapine, and pimavanserin. (43) In individuals with PIGD and TD PD, L-DOPA caused different tapping- induced coupling responses within the motor network. These results could not be explained by differences in the disease's duration or stage. While PIGD patients on and off medication did not exhibit any significant changes, there was a notable increase in effective connectivity between the left posterior putamen and other motor network locations when TD patients on medication were compared to TD patients not on

medication. The distinct reactions of identifiable PD motor subtypes to L-DOPA may be explained by underlying pathophysiology differences between them. (44) Gene therapy is a novel approach to PD treatment that is currently being investigated. Research is being done on both disease-modifying and non-disease-modifying transgenes. GABA and dopamine production pathways are the targets of non-disease modifying transgenes. The progression of the disease may be slowed by disease-modifying genes. Although the studies for both transgenes are still in their early stages, the results are encouraging [87]. Only the motor symptoms are addressed by gene treatments. (45). A non-selective dopamine agonist that stimulates both D1 and D2 receptors, apomorphine is prescribed to PD patients experiencing motor fluctuations and may also help with non-motor symptoms. It is the only antiparkinsonian medication that can control motor symptoms on par with L-DOPA, in contrast to other antiparkinsonian agents. (46)

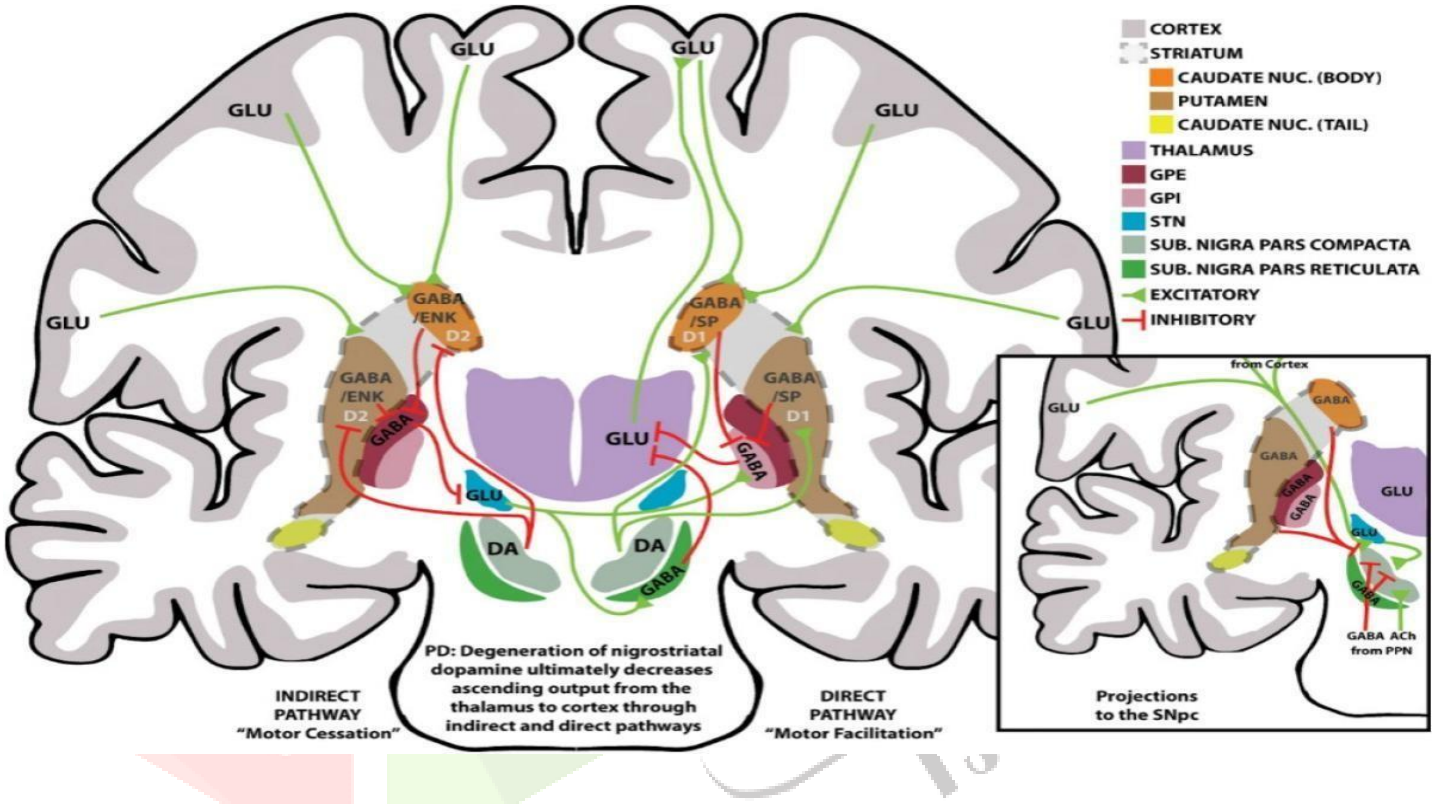


Fig.11.Pathway

An overview of the basic motor circuits and neuroanatomy of the basal ganglia is shown in Fig. Options for ablative surgery include subthalamotomy, which destroys the subthalamic nucleus (STN, blue), thalamotomy, which destroys the thalamus (purple), and pallidotomy, which destroys the global pallidus (GPE, GPI in maroon and pink, respectively). Procedures to lessen excessive inhibitory output from the substantia nigrareticulata (green) and internal globus pallidus (pink), as well as their corresponding pathways shown in red, can be bilateral or unilateral. Harris supplied the image. (47) Yoga's impact on oxidative stress, motor function, and non-motor symptoms in PD patients has been investigated and evaluated. Two 60-minute group-based lessons were conducted for the treatment group over the course of 12 weeks in a randomized controlled study that included both an immediate treatment group and a wait-list control group. Assessments of oxidative stress, motor and cognitive function, physical activity, sleep quality, and general quality of life were carried out at baseline, twelve weeks, and six months after the intervention.

Participants in this study had a mean age of 63 years (SD 8, range 49-75), a length of 4.8 years (SD 2.9, range 1-13), and a mild-to-moderate degree of illness. 85% of the participants attended at least 75% of the yoga classes, 20% attended all of the classes, and 90% of all participants were using dopaminergic drugs. Blood oxidative stress markers did not significantly differ between the treatment and control groups at the conclusion of the 12-week research. According to the UPDRS, the treatment group's motor function scores were higher, but their sleep

and physical activity levels were lower than thecontrol group based on the Longitudinal Aging Study Amsterdam Physical Activity Questionnaire and the Parkinson's Disease Quality of Life (PDQUALIF) Scale, respectively. Within-group comparisons showed improvements in motor function, cognitive function, and catalase levels; however, physical activity levels and the PDQUALIF's social and role function, sleep, and outlook domains were perceived to be worse at 12 weeks compared to baseline. Yoga may be a legitimate supplemental activity to help PD patients with their motor function, but additional research with bigger sample sizes is required to ascertain how yoga affects oxidative stress and non-motor symptoms. (48). To extend their effects, monoamine oxidase inhibitors (MAOIs), such as rasagiline or selegiline, and COMT inhibitors, such as entacapone, block the breakdown of dopamine and L-DOPA. The quantity of dopamine broken down in the synapse is decreased by MAOIs. COMT inhibitors stop L-DOPA from being converted into dopamine too soon by COMT. Before L-DOPA reaches the brain, it lessens peripheral loss. Because MAOIs have less adverse effects, need fewer doses, and might postpone the use of dopaminergic medications, they may be used initially to treat patients with moderate symptoms. Later on, they might also be used to treat particular symptoms like dyskinesias or tremors. (49) In PD, cognitive impairment has a major impact on quality of life. Although exercise has been recognized as a potential treatment, these deficits are still challenging to address with existing clinical medications. (50)

CONCLUSION

As one of the neurodegenerative diseases, Parkinson's disease poses a significant clinical problem. For patients with Parkinson's disease to receive the best care and have a higher quality of life, it is essential to understand the disease's symptoms, therapies, and
progressive long-term course. Treatments for medication-resistant tremor, increasing symptoms when the medicine wears off, and
dyskinesias include deep brain stimulation and levodopa-carbidopa enteral suspension.

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