Review Article

Unraveling The Enigma of Parkinson's Disease: From Molecular Pathways to Clinical Manifestations and Therapeutic Interventions

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ABSTRACT

"Parkinson's disease" is a progressive neurological condition characterized by tremors, bradykinesia, rigidity as well as other motor symptoms. It can also cause a variety of non-motor signs like sadness, anxiety, as well as sleep difficulties. The primary molecular pathogenic pathways encompassed misfolding and aggregation of α-synuclein, malfunction of mitochondria, reduced protein clearance, neuro inflammation, and oxidative stress. A variety of PD clinical manifestations are influenced by the involvement of dopaminergic and other neurotransmitter pathways. Parkinson's illness originates from environmental variables, lifestyle decisions, and genetic predisposition. Deep brain stimulation, dopamine replacement therapy, and other pharmaceutical interventions are used as treatment options to reduce symptoms. The degenerative nature of Parkinson's disease presents considerable obstacles in controlling its varied components, and there is presently no cure for the disease, despite continued research efforts.

Keywords: Tremor, Essential tremor, Bradykinesia, Freezing, Rigidity.

INTRODUCTION

PD, or Parkinson's disease, is a neurological condition that degenerates and can cause many signs, both motor and non-motor that can have varied degrees of functional impact. The focus of this review is on the clinical characteristics of PD that set it apart from other Parkinsonian illnesses[1]. People spontaneously synchronize their movements but insufficient internal rhythmicity is evident in PD patients[2]. Parkinsonism is a clinical syndrome that includes a variety of motor issues, including rigidity, flexed posture, bradykinesia, resting tremor, "freezing," and loss of reflexive posture. Parkinsonism is mostly caused by PD. It is a Parkinsonian syndrome that progresses gradually and typically commences initially on one side of the body and then spreads to the other half[3].Along with the conventional motor signs, non-motor signs (like constipation, anosmia, depression, and sleep disorder with rapid eye movement) also emerge during the prodromic/premotor stage of the disease, as the disease gets more severe, dysautonomia and cognitive impairment frequently predominate in the later stages of the illness. Currently being studied as possible treatments, an array of dopaminergic & non-dopaminergic drugs are being used clinically for treating the motor symptoms of PD[4]. For certain PD patients, STN DBS (Subthalamic Nucleus Deep Brain Stimulation) is a confirmed and efficient therapeutic option (PD). In order to establish the ideal therapeutic ranges, an in-depth study of the effects of stimulation parameters, such as stimulation strength, frequency, and pulse width, has been done from its inception[5].

The primary molecular pathogenic processes encompass α-synuclein misfolding and aggregation, malfunctioning of mitochondria, decreased clearance of proteins (connected to ubiquitin-proteasome systems and inadequate autophagy-lysosomal), neuroinflammation as well as oxidative stress. Approximately one percent of people above 60 and four percent of people above 85 have PD, which is the 2nd most widespread neurological disease after AD (Alzheimer's Disease).

HISTORY

The term clinical syndrome, or PD, refers to a group of symptoms that go beyond the motor & non-motor signs that James Parkinson first described in his 1817 "Essay on the Shaking Palsy." These symptoms include bradykinesia, rest tremor, postural instability, and rigidity. The identification of dopamine depletion as well as its function in animal models of PD, in addition to the identification of intracytoplasmic inclusion bodies, or "Lewy bodies," by Frederick Lewy in 1912 as a pathologic signature, are significant turning points in the etiopathogenesis of PD. Dopamine insufficiency and PD were linked by the groundbreaking research of Oleh Hornykiewicz and Arvid Carlsson beginning in 1957. The 1st trial of PD individuals receiving intravenous levodopa (1961) demonstrated clinical rescue, supporting the latter theory. George Cotzias' introduction of high-dosage levodopa therapy (1967) further supported this theory.

It wasn't until 1895 that the substantia nigra was proposed as being impacted by PD, following a case reported by Blocq & Marinesco of a tuberculoma in that region linked to hemiparkinsonian tremor. In order to complete his doctoral thesis, Tretiakoff evaluated the substantia nigra in 9 PD events, 1hemi parkinsonism event, and 3 postencephalitic parkinsonism events. He observed damages in this nucleus in every instance. Observing a lesion in the nigra on the opposite side, Tretiakoff concluded that in the hemiparkinsonian condition, the nucleus supported motor function on the body's

contralateral side. It has been observed that the substantia nigra, which bears this name due to its typical concentration of neuromelanin pigment, exhibits, loss of nerve cells, gliosis and depigmentation[6].

A physician named William Langston reported in 1982 that seven individuals in the San Francisco Bay Area were taking "synthetic heroin" as well as exhibiting Parkinsonian symptoms. Analyses additionally discovered “1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine” as the causative agent of this drug-induced Parkinsonism[7].It was shown that these chemical poisons the dopaminergic neurons in the substantia nigra. This finding greatly influenced research on the etiopathogenesis of PD as well as experimental treatments; as a result, extensive epidemiological research on potential occupational exposure to toxins as well as animal model pharmacological trials were conducted.

Since then, one of the main targets of DBS for the remedy of Parkinsonian motor signs has been the subthalamic nucleus. Rather than addressing the root cause of the disease, these therapy alternatives were created to lessen the symptoms of PD or the negative effects of antiparkinsonian medications. A deeper comprehension of the disease process is necessary to make significant progress in preventing or reducing the rate of cell loss in PD[8].

CLINICAL FEATURES

PD symptoms include both motor and non-motor ones. The acronym TRAP can be used to gather together the 4 primary characteristics of PD: postural deformities, tremor at rest, bradykinesia (orakinesia), as well as stiffness. Moreover, freezing (motor blocks) and flexed posture have been recognized as characteristic Parkinsonian features, with PD being the most common form. The most popular tool for assessing impairment as well as disability is the UPDRS (Unified Parkinson's Disease Rating Scale)[9,10]. Nigrostriatal dopamine gradually depleting is linked to the initial symptoms and indicators of PD, which comprise stiffness, rest tremors, and bradykinesia. Dopamine agonists as well as levodopa can typically be used to treat the striatal dopamine deficit causing these symptoms and indications[11].

- ***Motor Features***

1- Bradykinesia

James Parkinson used the word "bradykinesia" to characterize one of the defining characteristics of the disease which currently bears his name. The terms akinesia and hypokinesia are frequently used interchangeably with bradykinesia. In an absolute sense, bradykinesia is the slowness of an executed movement, whereas akinesia is the lack of accompanying movement or spontaneous movement (such as a facial expression) (e.g. arm swing during walking). The inability to start movements quickly and freezing are two other signs of akinesia. When motions are not only slow but also smaller than envisioned, as in the case of the patient's handwriting micrographia, it can be classified as hypokinesia. Other indications of bradykinesia comprise impaired blinking, drooling because of swallowing difficulties, face expression loss (hypomimia), reduced swing of the arms when walking, and dysphonic and monotonic dysarthria[12].

2- Tremor

The most prevalent and recognizable PD sign is rest tremor. Unilateral tremors are typically felt in the distal part of an extremity and manifest at a frequency of 4 to 6 Hz. Hand tremors are supination-pronation, often referred to as "pill-rolling," tremors moving from one hand to the other. PD individuals may also experience tremors in their chin, lips, legs, and jaw. Except that it rarely affects the voice, neck, or head, unlike essential tremors. A tremor that can be experienced inside the chest, belly, arms, or legs that is not visible is referred to as an internal tremor by certain PD patients. There are sporadic references to an internal vibration sensation in the literature, despite considering that this symptom has not been previously investigated[13]. Postural tremor is a regular sign of PD that is more noticeable and incapacitating than rest tremor and may be a sign of the illness before it is too late. Postural tremor associated with PD, also known as "re-emergent tremor," is distinct from crucial tremor in that it frequently manifests itself later when the individual adopts an extended horizontal posture. Since re-emergent tremor is responsive to dopaminergic therapy and arises at the same frequency as classical rest tremor, it is highly probable that it is an alternative form of the more typical rest tremor[14].

3- Rigidity

A consistent, steady rise in muscular tone that is perceived as unwavering resistance to passive movement is termed rigidity. Increased resistance is the hallmark of rigidity. This phenomenon, called the "cogwheel" effect, is most evident when accompanied by an underlying tremor & usually exists across the range of passive movement of a limb (rotation, extension, or flexion at a joint). It can occur both distally, as in the wrists as well as ankles, & proximally, as in the neck, shoulders, and hips. Reinforcing exercises, often referred to as Froment's manoeuvre, generally cause stiffness and are particularly beneficial in identifying mild events. They involve voluntary motions of the contralateral limb[15].Although it is misdiagnosed as arthritis, rotator cuff injury, or bursitis. Pain in the shoulder is among the most prevalent early signs of PD. Rigidity may also be accompanied by discomfort.

4- Postural Deformities

Additionally, axial rigidity, or stiffness of the trunk as well as the neck, can happen, leading to aberrant axial postures (such as scoliosis and anterocollis). Postural anomalies that result in flexed elbows and knees, along with a flexed neck and trunk posture, are often associated with rigidity[16].Abnormal postures known as striatal deformities of the foot as well as hand are frequent in people with advanced PD; they can also appear in patients with other Parkinsonian disorders or PD's initial stages. These

anomalies were identified by Charcot and Purves-Stewart, and they resulted in significant discomfort and functional disabilities. The term "striatal" refers to pathology in the neostriatum (caudate &putamen), which has been advised as the source of the abnormalities, although the pathophysiology of these abnormalities may not be understood. Misdiagnosis of hand abnormalities is common, especially when they present early and without cardinal parkinsonian symptoms, including bradykinesia, tremor, and rigidity because they mimic those of rheumatoid arthritis and equinovarus foot deformity[17].

5- Freezing

Freezing, sometimes referred to as motor blocks, is one of the most severe signs of PD. One kind of akinesia, or cessation of movement, is freezing. An extremely distressing frequently occurring Parkinsonian symptom is freezing of gait (FOG). Episodes of freezing are usually brief and transient, with a return to normal gait thereafter. While walking, freezing most frequently affects the legs, although it can also affect the arms as well as the eyelids[18].

Five subtypes of freezing have been identified: open space hesitation (i.e. a patient appears to have an episode of spontaneous freezing when travelling in an open area without any obvious trigger, such as a doorway), turn hesitation (while turning it seems as though the feet got trapped), start hesitation (i.e. when patient start walking, freezing is observed), and hesitation in tight quarters (when the patient passed through the narrow space, a freeze of gait is observed)& destination hesitation (when the patient got close to a target and it seemed like their feet were freezing). Levodopa treatment lessens the severity of episodes, which are more common in the OFF state[19].

- ***Non-motor Features***

Non-motor characteristics include abnormalities related to sleep, sensory processing, cognitive/neurobehavioral issues, and autonomic dysfunction.

1- Malfunction of the autonomic

One possible PD presenting symptom is autonomic failure. Features include erectile dysfunction, sweating malfunction, sphincter dysfunction, and orthostatic hypotension[20].

2- Neurobehavioral & Cognitive Disorders

Disturbances in neuropsychiatry can be just as impairing as physical symptoms. Apart from cognitive and affective disorders, a significant number of patients with PD display traits of obsessive-compulsive as well as impulsive behaviour. These traits include examining, hypersexuality, intense fascination with handling, sorting, compulsive foraging, binge eating, and arranging objects, and hypersexuality[21].

3- Sleep Disorder

While medication therapy for PD was formerly thought to be primarily responsible for sleep disruptions such as extreme drowsiness and sleep attacks, some physicians now consider that these symptoms are an inherent aspect of the condition[22]. About one-third of individuals with sleep behaviour disorder engage in dramatic, violent, and possibly harmful motor activities, such as yelling, swearing, grabbing, hitting, kicking, jumping, and other behaviours that may also include their bed partner. Although insomnia is common (.50% prevalence), especially in the case of sleep fragmentation, the frequency varies greatly throughout people[23].

4- Sensory Abnormalities

Even though they are widespread, sensory symptoms such as genital pain, discomfort, paresthesia, akathisia, mouth pain, and olfactory impairment (hyposmia) are sometimes mistaken as parkinsonian symptoms[24].

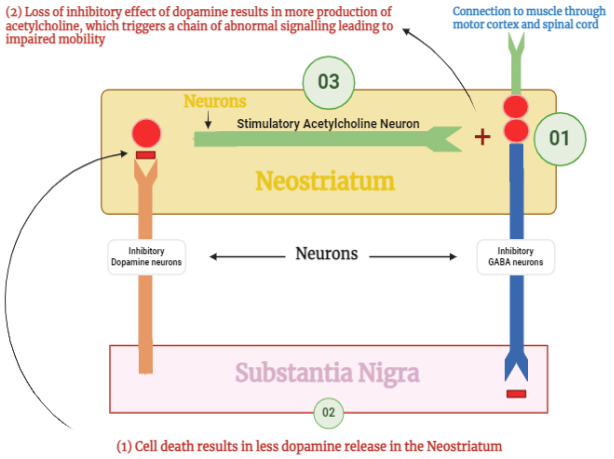

Figure 1: Flowchart of etiology of Parkinson disease

BIOCHEMICAL ASPECTS OF PD

Before 1957, it was believed that a deficiency in serotonin in the brain caused the Parkinsonian disease that reserpine causes in both humans and animals. But that year, Carlsson and associates found that L-5-hydroxytryptophan, the precursor to serotonin, failed to recover the parkinsonian state induced by reseipine in rabbits, but L-dopa did. Back then, it was believed that dopamine only had a role as a precursor to norepinephrine[25].Carlsson discovered the presence of dopamine in the brain in 1958 after devising a technique for its chemical assay. After this, the presence of dopamine was identified regionally in the brains of humans and animals**.** In 2000, Carlsson was finally granted, the Nobel Prize in Physiology and Medicine[26].It was discovered that norepinephrine was concentrated in the dorsal regions of the pons, oblongate medulla, and hypothalamus, which are located adjacent to the reticular formation. This finding is consistent with that about dog brains. Dopa was not restricted to any one area of the brain. There was no doubt that dopamine was localized. Significantly elevated levels of this amine were discovered in the putamen of the neostriatal caudate and lentiform

nuclei. These components are a part of the extrapyramidal structure. In addition to these nuclei, the extrapyramidal portions of the pallidum of the lentiform nucleus, the red nucleus, and the hypothalamus and thalamus also contain significant levels of dopamine. Carlsson proposed the link between dopamine present in the brain and Parkinson's disease during his presentation at the International Catecholamine Symposium in October 1958.Dopamine and norepinephrine levels in postmortem human brains were measured by Hornykiewicz in 1960, and the results indicated a deficiency in neostriatal dopamine in both PD and post encephalitic parkinsonism[27]. Several Swedish researchers were able to observe where the biogenic amines were localized cellularly via the development of fluorescence histochemistry; the cell bodies were found in multiple brain stem nuclei, additionally, their axons penetrated parts of the brain hemispheres. The axons of the dopamine-comprising cell bodies in the nigra's pars compacta terminated in the putamen and caudate. The substantia nigra of primates with experimental lesions showed a similar decrease in striatal dopamine[28].This marked the beginning of the modern era's understanding of dopamine's function in the brain and PD.

DIFFERENTIATING PARKINSON'S DISEASE AND PARKINSONISM

Combinations of any six distinct motoric traits—bradykinesia, loss of postural reflexes, stiffness, tremor at rest, freezing phenomena, and the flexed posture, in which the feet are momentarily "glued to the ground"—define parkinsonism. All six of these cardinal symptoms don't need to be present; nevertheless, before parkinsonism is diagnosed, at least two of them—bradykinesia or tremor at rest—should be present. There are four classifications for PD. Parkinsonism plus syndrome, primary parkinsonism, secondary parkinsonism, and neurodegenerative disorder. The predominant aetiology of parkinsonism is primary parkinsonism or PD. Three of the most helpful signs that one is most likely experiencing PD as opposed to another kind of parkinsonism are (i) Asymmetrical symptom onset (Parkinson's disease typically starts on one side of the body). (ii) tremor at rest (sometimes PD patients may not have rest tremor, but Parkinson plus syndromes rarely do); and (iii) Significant improvement in clinical symptoms with the correct administration of levodopa treatment (PD-plus syndromes usually do not show improvement with levodopa treatment). Essential tremor, sometimes mistaken for Parkinson's disease, can cause tremors that are often bilateral but can occasionally be unilateral. The tremor induced by PD. PD is a rest tremor, meaning it affects the body part when it is at rest. Essential tremor causes a tremor that occurs when the arm is extended in front of the body and becomes more intense while the arm is in use, such as during writing or doing the finger-to-nose test.

ETIOLOGY

Debate has arisen regarding the respective involvements of genetic factors as well as environmental/lifestyle variables in the pathogenesis of PD. At the start, the median age was 60 years, ageing being the primary risk factor for PD[29]. Incidence may vary due to variance in the occurrence of factors including caffeine consumption and smoking habits, with a greater frequency seen in men than in women (with a ratio between 1.3 to 2.0). Similar to previous neurodegenerative disorders, age-related biological malfunctions such as mitochondrial abnormalities, ubiquitin-proteasome and autophagy-lysosomal system dysfunction, genomic instability, telomere dysfunction, and epigenetic modifications may contribute to and facilitate the death of neurons[30].

1- Environmental risk factors

Clinical association studies have historically studied the possible cause-&-effect association among etiologic factors as well as disease using cross-sectional (community-based and hospital) or prospective (population-based) methodologies. Risk factors such as exposure to heavy metals and pesticides, working in agriculture, living in rural areas, experiencing traumatic head injuries, having a history of melanoma, consuming dairy products and well water, having type 2 diabetes mellitus (which can be managed with anti-diabetic drugs), and various other factors[31].

2- Lifestyle And Other Protective Factors

The two preventive factors that are consistently connected to a lower risk of PD are cigarette smoking and coffee intake. Since nicotine has been demonstrated to enhance dopamine release in the striatum as well as maintain dopaminergic function in experimental models, the other hypothesis connects nicotine to dopaminergic neuronal defence. It's also possible that cigarette smoke contains additional neuroprotective substances that haven't been found yet. Caffeine users had a relative risk reduction of PD of between 0.5 and 0.8 similar to smoking, and most studies have consistently shown a dose-dependent impact. It has been suggested that caffeine, an antagonist of the adenosine A2a receptor, protects neurons by preventing this receptor from functioning. Uric acid, a byproduct of purine metabolism, acts as an antioxidant with radical-scavenging capabilities. A meta-analysis of 13 research found that serum uric acid levels are lower in people with PD compared to control subjects. This trend is also observed in people with more advanced disorders compared to those in the initial stages of PD.

3- Genetics

The gene α-synuclein (SNCA), associated with PD, was identified in 1997 through twin research as well as the observation of families exhibiting dominant and recessive inheritance patterns. These findings supported the theory that PD has genetic roots. A year later, a Parkin (PRKN) mutation was discovered that was connected to the PD in its autosomal recessive form. Since the International Parkinson & Movement Disorders Society's classification of these genes using their names is preferable to the

complicated terminology of giving them a "PARK" number, we will stick with their suggestion[32].

PARK-SNCA (PARK1)

While PD is rarely caused by SNCA mutations, it has now been demonstrated that α-synuclein is essential in the development of PD. The function of α-synuclein, a 140 amino acid protein, in the normal brain, is not yet understood, however, it is associated with the following processes: (i) vesicle trafficking; (ii) vesicle docking as well as priming; (iii) vesicle fusion as well as neurotransmitter release; and (iv) axonal transport. Both nigral degeneration and levodopa-responsive motor impairment can result from overexpression of α-synuclein in transgenic mice. Dopamine modification (hazardous interactions between lipids and α-synuclein oligomers), pathogenic mutations, and excessive wild-type (multiplication) have all been used to demonstrate the toxicity of this protein. The clinical hallmarks of PD, Lewy bodies as well as Lewy neurites, are primarily composed of α-synuclein, which is a non-soluble, aggregated, fibrillar form. Even though SNCA mutations are uncommon, the detection of full gene triplication, duplication, and quadruplication offers significant insights into the underlying pathophysiology including SNCA protein. It also confirms previous findings that SNCA promoter polymorphism raises the risk of sporadic PD[33].

PARK-Parkin (PARK2)

The most prevalent autosomal recessive PD-related gene is parkin (PRKN); approximately half of the individuals with early-onset PD are compound heterozygotes for PRKN. Dystonic gait, leg tremor at rest as well as while standing, dopa-responsive dystonia, cervical dystonia, festination, freezing, significant sleep benefit, retropulsion, ataxia, hyperreflexia, dysautonomia and peripheral neuropathy, are possible presentation symptoms of the disease. Levodopa-induced dyskinesia usually develops early and complicates an excellent levodopa response. Lewy bodies are rare and the dorsal tier is usually well maintained at autopsy, However, the substantia nigra pars compacta typically experience neuronsloss[34]. A key mechanism of illness is impaired mitochondrial function. Mitochondrial activities are regulated by several genes linked to familial types of Parkinson's disease: An avenue for controlling mitochondrial quality involves the interplay between Parkin as well as PINK-1. The serine/threonine kinase PINK1, which "marks" damaged mitochondria as well as starts the mitophagy process, recruits the E3 ubiquitin ligase Parkin. PARK 7 encodes a protein of 189 amino acids called DJ-1. DJ-1 regulates the calcium “flux in the mitochondrion, shielding the cell against dopamine toxicity and oxidative stress brought on by the pace-making activity of dopaminergic neurons. There have been reports of mitochondrial DNA alterations, most likely of somatic origin, in the SNpc of PD brains[35].

PARK-LRRK2 (PARK8)

The most prevalent autosomal dominant PD-related gene is LRRK2. Age-dependent penetrance of a common mutation (G2019S) has been observed in both familial as well as sporadic PD cases. With” reduced RBD and comparatively retained olfaction, the majority of LRRK2 carriers have a late onset that mimics typical PD as well as are clinically identical to those who are not carriers. However, their course appears to be more benign, mostly characterized by the PIGD (postural instability gait difficulty)phenotype. dementia, Orthostatic hypotension, corticobasal syndrome, hallucinations, and primary progressive aphasia are examples of atypical characteristics.

LRRK2, or dardarin, is a big protein consisting of 2527 amino acids. which means tremor, is involved in autophagy, cytoskeletal function, vesicular trafficking, protein synthesis, and interaction with mitochondrial proteins. It may also affect the immune system. The striatal medium-sized spiny neurons, as well as macrophages and microglia, have elevated expression of LRRK2, which may indicate a role in the inflammatory pathway[35].

PARK-GBA

The glucocerebrosidase (GBA) gene, located on chromosome 1q21, codes for the lysosomal enzyme glucocerebrosidase, which is essential for the hydrolysis of sphingolipids and breaks down glucocerebroside into glucose and ceramide. Regarding PD, the most significant genetic risk factor is mutations of the GBA gene, which can be heterozygous, homozygous, or compound heterozygous. These mutations increase the risk of PD by more than five times compared to the general population. p.N370S, p.E326K, and p.T369 M are common pathogenic variants that have impact sizes ranging from 2.6 to 0.9 years reduction in age-at-onset.

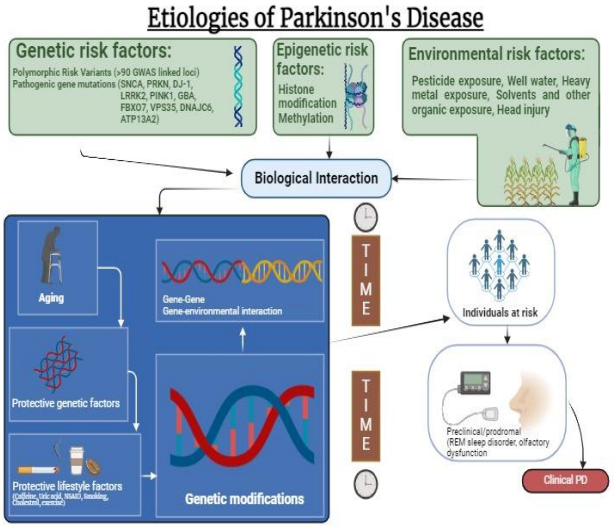

Figure 2: Etioloy of Parkinson Disease

It has been suggested that lysosomal enzyme action is hampered by glucocerebrosidase loss of function, which is followed by α-synuclein buildup as well as aggregation. It

has been suggested that lysosomal enzyme action is hampered by glucocerebrosidase loss of function, which is followed by α-synuclein buildup and aggregation[36].

PATHOPHYSIOLOGY

Lewy Bodies and dopaminergic neuron loss, which results in SNpc depigmentation, are the primary pathological characteristics of PD. Lewy Bodies are round, eosinophilic, intraneuronal inclusions with a pale peripheral halo and a hyaline core that are made up of over 90 proteins. Alphasynuclein & ubiquitin are the main proteins that compose Lewy bodies; it tends to misfold, turn into insoluble, as well as scan create amyloid aggregates rich in beta sheets, which can build up to create intracellular inclusions[37].

In this process of aggregation, the intermediaries are toxic oligomeric as well as proto-fibrillar forms, causing damage to biological membranes [38], the cytoskeleton, altered synaptic function, mitochondrial, lysosomal and proteasomal, and neuronal degeneration. It has been predicted that up to 60% of dopaminergic neurons may already be destroyed at the time of diagnosis.

Alpha-synuclein deposition and Lewy body formation have been proposed to happen sequentially, starting from the anterior olfactory nucleus, the glossopharyngeal as well as vagal nerves' dorsal motor nucleus, & then progressively moving to the brainstem, allocortex, mesocortex, and finally the neocortex[39].The propagation of pathogenic changes that have been previously reported is probably caused by alpha-synuclein's prion-like tendency to spread throughout neurons. Also, some evidence points to the possibility that the gut microbiota may have an impact on alpha-synuclein aggregation, which could begin in the stomach's autonomic plexi and spread laterally[40].

Dopamine depletion has amazing neurophysiologic consequences in PD patients and animal models. A proposed model depicts the activity of the basal ganglia in both normal as well as dopamine-deficient conditions. According to this model, a dopamine deficiency causes striatal dysfunction, which results in (i) diminished direct route activity, which passes “from GABAergic striatal neurons to the integral segment of the globus pallidus (GPi) as well as substantia nigra pars reticulata (SNpr); and (ii) increased drive through the indirect pathway, which passes through the external segment of the globus pallidus (GPe) and subthalamic nucleus (STN). As a result, there is a disruption in the activity of the basal ganglia output structures (GPi and SNpr)” as well as the thalamocortical motor system and the pedunculopontine nucleus, two brain stem motor centres. Parkinson's disease is known for its restricted range of motion and difficulties in initiating movements, which is believed to be caused by this disturbance[41].

EPIDEMIOLOGY

PD is a disorder related to ageing that steadily rises in incidence and prevalence as people get older. However, the myth that PD exclusively affects the elderly is untrue. Of those affected, 5–10% had an age of onset before 50, while nearly 25% had an age of onset before 65. "Young-onset Parkinson's disease" is the term used to describe affected individuals whose age of onset is less than 40 years old (or maybe even younger than 50 years old). Several other demographic characteristics have been linked to a rising risk of PD, in addition to advanced age, male gender, and European ancestry. There has been a lot of interest in the idea that being exposed to environmental pollutants could increase the chance of getting PD. Since the identification in 1983 of a cohort of individuals who, after consuming intravenous substances tainted with MPTP (Methyl-Phenyl-Tetrahydropyridine), developed a PD-like condition. There is a doubling of the predicted risk of disease as a result of pesticide exposure. Numerous mitochondrial poisons promote dopaminergic cell death in animal models, which may be compatible with this discovery. These toxins include MPTP, the herbicide paraquat, and the insecticide rotenone[42].

However, there isn't any epidemiological proof to back up the claim that exposure to heavy metals, like manganese and iron, at work or through other means raises the danger of PD. Numerous research investigations have also assessed dietary and behavioural factors; smoking cigarettes and drinking coffee are linked to decreased susceptibility to PD. Crucially, though, an association between incidence and result does not always indicate causality. The function of the basal ganglia in reward systems as well as impulse control may make people with PD less likely to engage in addictive behaviors[43].

IMPACT OF BIOLOGICAL SEX ON PD PATHOPHYSIOLOGY

The fact that postmenopausal women and men experience Parkinson's disease at similar rates suggests that estrogens are mostly responsible for the sex-based variations in the disease, providing disease prevention. “Sex differences are now visible in brain regions and functions that were not previously supposed to be affected by such variations, and it is significant because sex hormones affect every part of the male and female brains. These results open up new avenues for understanding gender-related behaviour & functions.

Dopaminergic neurodegeneration

Compared to other neuronal types, dopaminergic neurons in the substantia nigra are extremely sensitive to stressors. Numerous factors, including high oxidative burden during dopamine metabolism, high iron content, excitotoxicity, & poor mitochondrial mass, can be attributed to this sensitivity. Therefore, the distinct susceptibility of dopaminergic neurons to degenerate may be explained by differences in sex in these parameters. A sex-specific genomic signature was found through gene expression research in human SNc dopamine neurons from control as well as PD subjects”. While increased genes in males produce proteins related to the pathophysiology of PD, such as PINK1 and alpha-synuclein, upregulated genes in

females are predominantly engaged in neuronal maturation as well as signal transduction. Except for the insular cortex, all regions studied (the dorsal and ventral striatum) showed a greater D1:D2 ratio in females than in males[44]. This suggests that having a D1 dominance may make a person resistant to certain diseases, like addiction, but susceptible to others, like anxiety. Male neurons are more susceptible to stimuli that cause degeneration than female neurons when it comes to dopaminergic cells. The fundamental reason for the decreased susceptibility shown in the female brain is the unique result of estradiol on dopamine metabolism. Estradiol is known to enhance the production, reuptake, release, and dopamine turnover. Furthermore, by interacting with mGlu5 and estradiol receptors, this hormone increases amphetamine-stimulated dorsolateral striatal DA release in ovariectomized rats[45].

Neuroinflammation

The pathogenesis riddle of PD includes neuroinflammation as a key component. According to available research, ageing may impair the physiological functions performed by astrocytic and microglial cells, which could lead to the development as well as progression of PD. With their anti-inflammatory qualities, estrogens may play a role in both sex-related risk and Parkinson's disease development throughout the lifespan of an individual's life[46].

Specifically, male microglia that have been estrogen-primed exhibit altered immune function by being better able to respond to inflammatory stimuli. Male microglial transcriptomes are more developmentally advanced than female microglia, and Hanamsagar & coll. have shown that the processes governing development as well as immunological reactivity in microglia are dissociable in males vs. females. Numerous investigations conducted on animal models of PDhave demonstrated that estrogens' neuroprotective and symptomatic effects stem from their capacity to reduce microglia activation as well as modify microglia polarization towards a cytoprotective phenotype. Estrogens have been shown in multiple animal models of PD to have a neuroprotective & symptomatic effect because they can reduce microglia activation as well as modify microglia polarization toward a cytoprotective phenotype. Astrocytes exhibit sex differences in both healthy as well as pathological conditions, just like microglia do. Different inflammatory challenges, including lipopolysaccharide treatment, elicit different responses from male and female cortical astrocytes, resulting in elevated levels of specific inflammatory factors. Following exposure to lipopolysaccharide (LPS), male astrocytes exhibited increased expression of IL6, TNFα, and IL1β, while female astrocytes generated more Interfon-inducible protein 10[47]. When the physiologically significant oxygen tension is low, male astrocytes can breathe at a higher maximal respiration than female astrocytes. The defensive properties of estrogenic drugs are facilitated by astrocytes. Hormones and cognition may be positively correlated, as evidenced by the demonstrated involvement of estrogens in hippocampus plasticity as well as how estrogens affect memory. Estrogens may regulate neurogenic inflammation by blocking NF-κB activity, which may protect against memory disorders. Astrocytes can change metabolic as well as brain plasticity processes that are crucial for memory and learning by up-regulating aromatase in a cytokine-dependent manner and releasing cytokines[48].

Oxidative stress

Because of the key roles that mitochondria perform, their high metabolic rate, as well as their increased susceptibility to oxidative brain injury, maintaining mitochondrial homeostasis is essential for the survival and functionality of neurons. Due to exclusive maternal transmission, mitochondria exhibit strong sex-specific behaviour & affect males and females differently. Gender has an indiscriminate effect on every mitochondrial function. Research carried out on animal models and human postmortem samples revealed that female neurons are more functionally capable and exhibit higher levels of electron transport chain activity than male neurons. Regardless of age or estrus cycle, brain mitochondria from female rats have been shown to experience less oxidative stress and damage than those from male rats[49].Because female brain mitochondria have a lesser capacity for absorbing calcium than male brain mitochondria, this can have an adverse effect on the calcium buffering function of the mitochondria and, consequently, on cell homeostasis. On the other hand, the female gender has a favourable impact on redox oxygen species production and cell respiration. A paramagnetic pigment called neuromelanin functions as a scavenger by binding redox-active metal ions like iron or by auto-oxidizing catecholamines, which can remove potentially harmful chemicals. For many years, it has been understood that iron and estrogens interact in PD. There is evidence from experiments and epidemiology that suggests estrogens regulate iron metabolism. Women were less likely to develop Parkinson's disease (PD) at the same plasmatic amounts of iron, according to a human investigation. It has now been established that the effects of estrogen on iron metabolism are exploitative. It has now been established that the mechanisms by which estradiol affects iron metabolism vary for men and women.

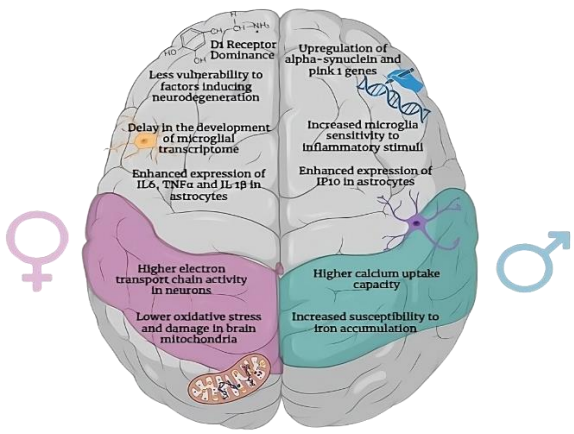

Figure 3: Impact of biological sex on PD pathophysiology

GPER1 mediates the suppression of estradiol's effects on iron overload-induced autophagy in men, whereas estrogen receptors cause lipid peroxidation in women. In astrocytes, estrogen would enhance the expression of the iron importer DMT1 (Divalent Metal Transporter 1) and iron exporter ferroportin 1 (FPN1), while in neurons, the down-regulation of iron regulatory protein might be responsible for the rise expression of FPN1 and declined DMT1[50].

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

For the most part, Parkinson's disease diagnosis is clinical. For PD, the Movement Disorders Society has updated the diagnostic standards.

SECONDARY PARKINSONISM

Lesions of the basal ganglia resulting from several causes, including ischemic, neoplastic, or infectious causes, can cause secondary Parkinsonism. When these symptoms appear suddenly and coexist with other symptoms, a diagnosis other than PD should be considered. Parkinsonism can be brought on by exposure to toxins (manganese, carbon monoxide), medications (metoclopramide, tetrabenazine, amiodarone, lithium), or a combination of these. DIP (Drug-Induced Parkinsonism) is the 2nd most prevalent cause of parkinsonism after PD. Symmetric symptoms, oro-mandibular dyskinesias, and a lack of response to levodopa can help distinguish DIP from PD, however, DIP's motor characteristics can also resemble PDs. Though confounding variables like age, smoking, and cognitive impairment might make things more difficult, hyposmia appears to be the most accurate NMS to distinguish between PD as well asDIP[51,52].

ESSENTIAL TREMOR

Asymmetrical presentation of postural and/or action tremor at a frequency of 5–12Hz, affecting the hands, head (“yes-yes” or “no-no”), and/or voice, is what defines ET. While rest tremor is possible, unlike Parkinson's disease, it gets worse when you move. Instead of micrography, as in Parkinson's disease, patients have tremulous handwriting. Apart from tremors, there have also been reports of minor cerebellar indications, cognitive impairment, mental problems, and sensory difficulties on occasion. Although primidone, propranolol, and alcohol can lessen symptoms, they are ineffective for Parkinson's disease (PD), which often progresses slowly. Inheritance of ET is autosomal dominant, &individuals frequently report a positive familiar history. Misdiagnosis is comparatively prevalent, and several overlapping symptoms between PD and ET have been observed[51,52].

ATYPICAL PARKINSONISM

A neurodegenerative condition known as MSA (Multiple System Atrophy) is categorized by autonomic failure, parkinsonism, and/or cerebellar symptoms. Akinetic-rigid parkinsonism differs from PDin that it has a symmetric distribution as well as shows little to no response to levodopa; hyperreflexia and extends or plantar responses are examples of pyramidal signs; cerebellar signs include dysarthria, nystagmus, dysmetria, and ataxia; & oculomotor dysfunction includes dysmetric saccades, impaired smooth pursuit movements, and suppression of the vestibuloocular reflex are possible symptoms of MSA. Patients rarely have a classic resting tremor; instead, they may exhibit a jerky poly-mini myoclonus. Orofacial dystonia or neck (antero- or laterocollis) might happen, particularly after using levodopa. Uro-genital, respiratory (sleep-related breathing disorders, stridor, respiratory insufficiency), cardiovascular (orthostatic hypotension and its symptoms, including postural as well as syncope dizziness), gastrointestinal, and sudomotor symptoms are among the dysautonomic features that are frequently observed in the early stages of the disease. Later on in the illness, dementia may develop. Pathologically speaking, MSA is a synucleinopathy; the olivopontocerebellar and/or striatonigral systems are more frequently affected by the neurodegeneration.

PSP, or progressive supranuclear palsy, is a disorder with multiple subtypes. The most common subtype is referred to as Richardson Syndrome, and it is characterized by an axial akinetic-rigid parkinsonism that does not respond well to levodopa. Other symptoms include gait abnormalities (broad-based gait and freezing), postural instability, postural abnormalities (head and trunk hyperextension/retrocollis versus camptocormia in Parkinson's disease), as well as falls since the disease is early in its course rather than late, as in PD. One distinctive feature of PSP is supranuclear palsy of vertical gaze, which is not present in PD. Other signs of oculomotor dysfunction such as apraxia of eyelid opening, which causes the frontalis muscle to over activate in response, resulting in the typical "surprised" expression and slowing of vertical saccadic movements, especially downward.

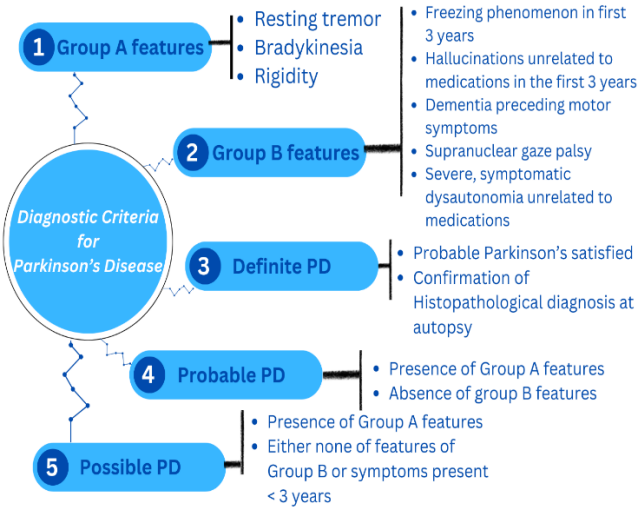

Figure 4: Diagnostic criteria for Parkinson disease

The most prevalent motor symptoms of CBD (Corticobasal Degeneration) are bradykinesia and asymmetric rigidity, which often affect one limb. In addition, unlike Parkinson's disease (PD), dystonia and myoclonus—which are frequently distal and stimulus-sensitive—can also occur.

Roughly 50% of patients report experiencing the "alien limb phenomenon," which is a limb that may involuntarily take on positions, grasp items, or interfere with the movements of the unaffected limbs. Seldom does a tremor occur, and when it does, it is an action/postural tremor as opposed to a resting tremor like in Parkinson's disease. Additionally, cortical characteristics that are typically lacking in PD like apraxia, cortical sensory loss, and dementia that typically affects frontal and parietal processes are also present in CBD[51,52].

TREATMENT

Drugs Used In PD

1- Dopamine Precursor- Levodopa

Restoring dopamine levels, imitating dopamine function, and countering the excitatory effect of cholinergic neurons are the three main goals of pharmaceutical therapy for Parkinson's disease. Inside dopaminergic neurons, dopamine is synthesized in two steps process. Firstly, with the help of tyrosine hydroxylase, the amino acid tyrosine gets converted into levodopa. In the second step, the L-Dopa is quickly decarboxylated by AADC (Aromatic L-Amino Acid Decarboxylase) and converted into the neurotransmitter called dopamine. Physiological stimuli release dopamine from the synaptic vesicle and cause it to bind to the dopamine receptor located on presynaptic neurons in the extracellular space. Ultimately, extra dopamine in synapses is taken up by neurons or glial cells and processed by COMT (Catechol-O-Methyltransferase) and MAO (Monoamine Oxidase).

The BBB (Blood-Brain Barrier), is a densely packed layer of endothelial cells that prevents chemicals from passing through to the brain. L-Dopa can pass over this barrier, while DA is unable to do so.

2- Peripheral Decarboxylase Inhibitors- Carbidopa & Benserazide

L-dopa encounters a significant challenge when it comes to peripheral metabolism. Two significant enzymes in the periphery break down levodopa before it reaches the brain: peripheral dopa-decarboxylase (DDC), which converts L-dopa to dopamine, and COMT, which converts L-Dopa to OMD (3-o-methyldopa). L-Dopa must be administered with carbidopa to inhibit DA decarboxylase as well as limit the metabolism of L-Dopa in the periphery.

3- COMT Inhibitor- Entacapone & Tolcapone

COMT convert DA into 3-MT(3-Methoxytramine). Entacapone is another drug that, when administered in conjunction with L-Dopa and carbidopa, inhibits peripheral COMT and extends the duration of L-Dopa's activity in the brain. An amino acid transporter carries L-dopa over the blood-brain barrier. L-dopa is efficiently turned into dopamine inside the brain to supplement decreased dopamine levels in the midbrain.

4- MAO-B Inhibitors- Selegiline & Rasagiline

DA is also susceptible to breakdown by COMT &MAO-B which convert DA into 3-MT(3-Methoxytramine) & DOPAC (3,4-dihydroxyphenylacetic acid) correspondingly. Another medication that selectively inhibits MAO-B is Selegiline and Rasagiline. In comparison to Entacapone & Tolcapone, Selegiline & Rasagiline can better penetrate the BBB & thus can act on both CNS & PNS.

5- Dopaminergic Agonists- Bromocriptine, Ropinirole, Pramipexole

These drugs work to increase dopamine levels in the brain by preventing dopamine from being metabolized. The hallmark of PD is the progressive loss of neurons that produce dopamine, causing a decrease in the cells that can release dopamine. Some drugs mimic DA and directly stimulate dopamine receptors in the brain.

6- Central Anticholinergics- Trihexyphenidyl, Procyclidine, Biperiden

In PD, Depletion of dopamine leads to elevated acetylcholine release, which subsequently stimulates muscarinic receptors situated on the neurons involved in regulating smooth muscle motor control. Excessive activation of these neurons by acetylcholine leads to tremors and stiffness. Antimuscarinic drugs disrupt muscarinic acetylcholine receptors and cholinergic nerve function. Therefore, these anticholinergic medicines help to rebalance the levels of acetylcholine and dopamine, potentially enhancing the symptoms of Parkinson's disease.

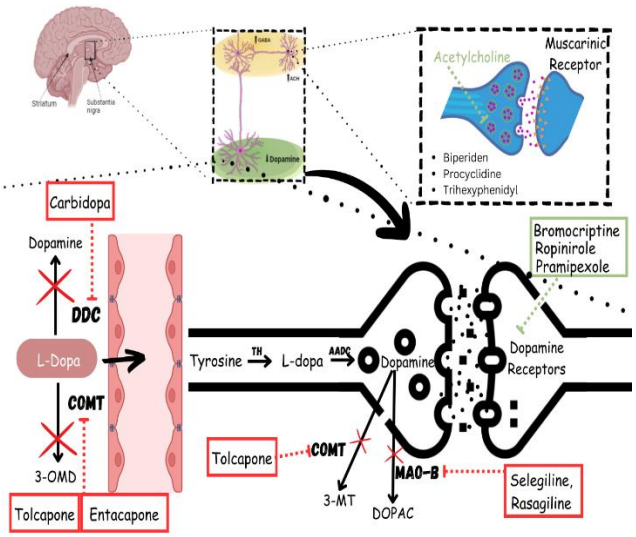

Figure 5: Mechanism of action of drugs acting on Parkinson diseases

7- Glutamate Agonist- Amantadine

It prevents dopamine reuptake, facilitates presynaptic DA release & blocks glutamate NMDA receptors. The potential of glutamate and adenosine 2a receptor modulators (NEU-240, Foliglurax and Mavoglurant, Dipraglurant,) to treat dyskinesias is currently being investigated. Istradefylline, an adenosine A2a receptor modulator, has already been

accepted in Japan, whereas Preladenant, an adenosine 2a receptor modulator, has not shown clinical efficacy[53].

DEEP BRAIN STIMULATION

The foundation of DBS is the delivery of high-frequency, long-term direct electrical current to a target, which, depending on clinical criteria, maybe the thalamus, the STN (the most frequently utilized target in PD), or the GPi(Globus Pallidus Internus). DBS is an additional treatment option for advanced Parkinson's disease. A recent theory suggests that DBS produces its therapeutic benefits by separating input and output signals in the stimulated target and disrupting the abnormal information flow across the cortico-basal ganglia loop. DBS appears to work through a combination of excitatory and inhibitory actions. STN-DBS is useful in lowering antiparkinsonian medication dosages, managing motor symptoms and consequences, managing some NMS, reducing disability, and enhancing HRQoL (Health-Related Quality of Life). In individuals with advanced PD, randomized controlled trials have demonstrated that STN-DBS is more effective than pharmaceutical treatment in lowering motor problems and enhancing HRQoL. A positive outcome with DBS is dependent on a number of variables that interact, including surgical technique, patient selection, pharmaceutical therapy modification, postoperative stimulation parameter setting, and electrode placement. The most critical factors to take into account are age, disease duration, type and severity of levodopa-unresponsive symptoms, levodopa responsiveness, brain MRI findings, cognitive and psychiatric issues, and comorbidities. The effectiveness of DBS depends on the careful selection of patients. It ought to be completed by a multidisciplinary team with DBS experience, adhering to the CAPSIT-PD core assessment program for surgical interventional therapy in PD[54].

DBS side effects include adverse hardware and intraoperative events, psychiatric symptoms, worsening cognitive function, and ocular, as well as speech disturbances. In addition, motor signs—like falling, freezing, and axial signs—that are not improved significantly by levodopa do not significantly improve with DBS[55].

DRUGS APPROVED BY USFDA

S.No.	Drugs	Approval Year	Approval Body	Formulation	Dose	Route of administration	References
1	Carbidopa-levodopa eternal suspension	2015	USFDA	Suspension	4.63-20mg	infusion	56
2	Rivastigmine	2007	USFDA	Oral capsules, transdermal patches	3.12mg/day	Oral or infusion	57
3	Istradefylline	2019	USFDA	Tablet	20-40mg (without food)	oral	58
4	Opicapone	2016 2020	European commission USFDA	Tablet, capsule	25-50mg	oral	59

CONCLUSION

PD is a progressive neurological disease that presents with a variety of motor as well as non-motor signs. Although the natural course of PD varies, people with late-onset and PIGD (postural instability & gait disorder) tend to deteriorate more quickly. There have been reports that the standardized mortality ratio varies from 1 to 3.4. Clinicians must possess a comprehensive knowledge of the clinical signs of PD to differentiate it from comparable conditions, as there are currently no conclusive diagnostic tests for the condition. Methods of neuroimaging used to differentiate PD and other Parkinsonian illnesses. For certain Parkinson's disease patients, DBS of the STN is an efficacious therapy option. While PD symptoms can be lessened, the illness cannot be completely cured. PD is a degenerative illness in which fewer cells can produce dopamine and fewer neurons produce dopamine. Dopaminergic medications directly excite dopamine receptors in the brain by imitating dopamine.

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