Detailed insight into the pathophysiology and the behavioral complications associated with the Parkinson's disease and its medications

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Abstract

Background: The loss of dopamine neurons in the substantia nigra, as well as other mostly catecholaminergic neurons, causes many of the motor symptoms that define Parkinson's disease. Parkinson's disease is commonly thought of as a movement disorder, the significant prevalence of psychiatric complications such as cognitive impairment, and psychosis suggests it should be considered a neuropsychiatric illness, and all behavioral complications are linked to growing disability and the medication.

Main body: Apart from the disease-induced abnormalities, there are several other side effects of the disease and also from the medication used to prevent the disease. This article focuses on the pathogenesis of Parkinson's disease and also the behavioral abnormalities caused by the disease and its medication. The study's data were gathered by searching several review articles and research papers from a variety of sources, including Elsevier, PubMed, Research Gate, Journal of Pharmaceutical Science, etc., from the year 1985 to 2021. Parkinson's disease is a neurodegenerative disease caused by a variety of complex processes. It is responsible not just for motor symptoms, but also for a variety of behavioral symptoms that can arise as a result of the disease and/or medication.

Conclusion: Only symptomatic drugs are available; thus, finding treatments that directly address the disease mechanisms causing Parkinson's disease is essential. To alleviate the disease's burden on patients and their families, better treatments for the neuropsychiatric repercussions of Parkinson's disease are required.

Keywords: Parkinson's disease, Neurodegeneration, Mitochondrial dysfunction, PINK1, SNCA, Dementia

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Graphical Abstract
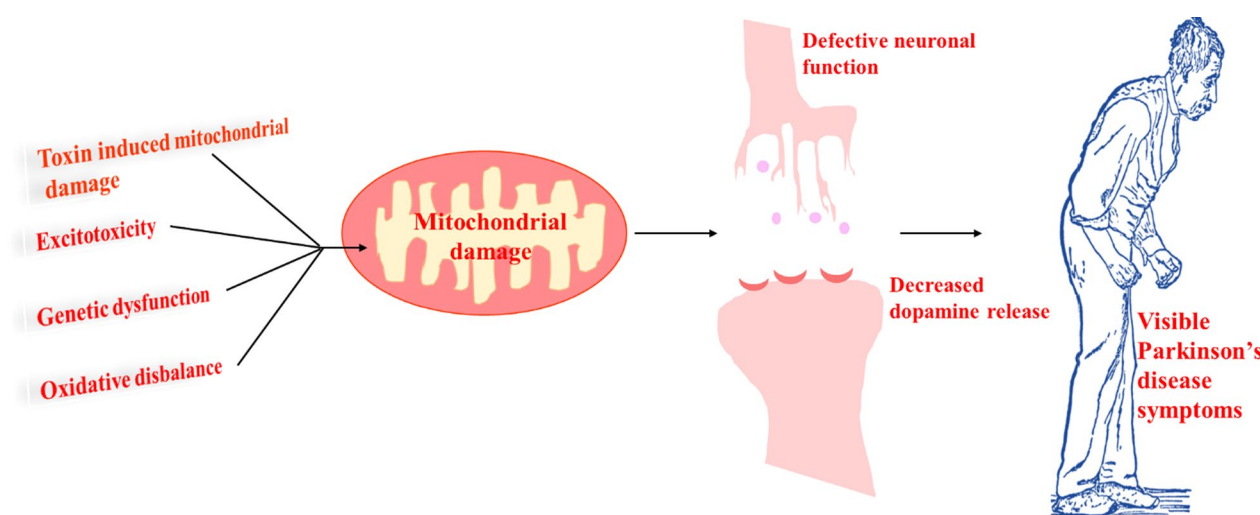
Background

"Neurodegeneration" etymologically consists of the prefix "neuro", which means the neurons or the nerve cells, and "degeneration", which means the loss of the structure and the function. So overall, neurodegeneration is a process of the loss of the structural and functional efficacy of the neurons. However, although it is a generally used word with a basic definition, the precise definition and depth of this term are considerably more. As a result, neurodegeneration is a collection of many degenerative dysfunctions that predominantly impact the body's neurons. As a neurodegenerative condition progresses, individuals experience a variety of symptoms. There are hundreds of neurodegenerative diseases estimated currently with few of them overlapping with each other pathologically and clinically [1].

Main text

Parkinson's disease

Parkinson's disease (PD) is a common adult-onset neurodegenerative disease that is regarded as the second most chronic and progressive condition. It is marked by continuous degeneration of nigrostriatal dopaminergic neurons. Dopamine (DA) deficiency is considered the main cause of Parkinson's disease [2–4].

The typical clinical symptoms of Parkinson's disease are the combination of motor disorders such as tremor, bradykinesia, loss of posture, and muscle rigidity [5]. Apart from the motor symptoms, many people with Parkinson's disease have other symptoms that are categorized as non-motor. Anxiety, fatigue, sleep disturbances, sadness, constipation, bladder and other autonomic abnormalities, sensory complaints, reduced thinking capability, diminished motivation and apathy, sensory complaints, and a decreasing cognition that can proceed to dementia are some of these symptoms. Parkinson's disease is a slowly progressing condition that commences slowly and gradually transforms into severity. It usually affects one side of the body before spreading to the opposite side. The disease progression is slow, but if it is left untreated over time, it results in severe immobility. Before the substantia nigra (SN), other brainstem regions, such as the olfactory nucleus, are subjected to pathological changes; the cerebral cortex is impacted later in the disease [6]. Parkinson's disease is increasingly recognized as a cause of cognitive, behavioral, sensory, and autonomic abnormalities, in addition to its well-known mobility condition. Cognitive impairment is now acknowledged as a prevalent symptom of Parkinson's disease [7], notwithstanding James Parkinson's original claim that intellectual function was retained in the "shaking palsy" [8]. Cognitive deficits are present in a high proportion of individuals with Parkinson's disease at the time of diagnosis, and they affect the majority of patients as the disease progresses.

However, the pathogenic pathways that cause Parkinson's disease are well established yet under progression, many researchers have considered a few factors such as the biochemical and genetic factors as the main cause of the disease. Mutations in particular genes, such as

α-synuclein and parkin, observed in rare, family cases of Parkinson's disease, suggest abnormal protein aggregation, whereas the mitochondrial dysfunction has been linked to biochemical factors.

Parkinson's disease also known as primary parkinsonism is the most common cause of parkinsonism as opposed to the other three types of parkinsonism such as drug-induced parkinsonism also known as postencephalitic parkinsonism. Secondary parkinsonism plus other neurological features are also known as Parkinson-plus syndromes, and lastly, heredodegenerative disorders in which parkinsonism is merely one symptom of a hereditary degenerative illness [9].

Pathogenesis of Parkinson's disease

Parkinson's disease is now commonly recognized as a multifactorial, complicated disease influenced by a variety of genetic, biochemical, and environmental factors. It affects numerous functional systems, not just the motor system, and multiple neurotransmitter systems, not just the dopaminergic system. The pathophysiology in each of the targeted neuron groups is identical, with intraneuronal Lewy body inclusions and lower numbers of surviving neurons, oxidative stress, mitochondrial dysfunction, excitotoxicity, and altered chemical conductance implying a consistent neurodegenerative mechanism. Mitochondrial dysfunction has been implicated as a key illness component because the majority of genetic PD

loci are directly linked to mitochondria, whereas oxidative stress and inflammation all play a role in the etiology of Parkinson's disease, according to epidemiological and experimental research.

Mitochondrial dysfunction in Parkinson's disease

Mitochondria are clusters of free-floating organelles in the cytosol, also known as the cell's powerhouse. Mitochondria's primary job is to produce energy in the form of adenosine triphosphate (ATP). Mitochondria play a role in lipid and amino acid metabolism. They also store pyruvate oxidation intermediates and Krebs cycle products [10, 11]. PD is caused by defects in mitochondrial respiration. The discovery that MPP+, the active metabolite of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) which selectively inhibits complex I of the mitochondrial electron transport chain, induces an acute parkinsonian illness has emphasized the significance of mitochondria in PD [12–14] (Fig. 1).

Various environmental toxins also act by inhibiting complex I and cause defects in the mitochondrial electron complex and reduction in the mitochondrial movement. This leads to an increase in mitochondrial permeability. 'Electron leaks' can also be seen at numerous points along the mitochondrial electron transport chain. These electrons further react with the molecular oxygen and the reactive oxygen species (ROS) of various types such as hydrogen peroxide (H_2O_2) and superoxide
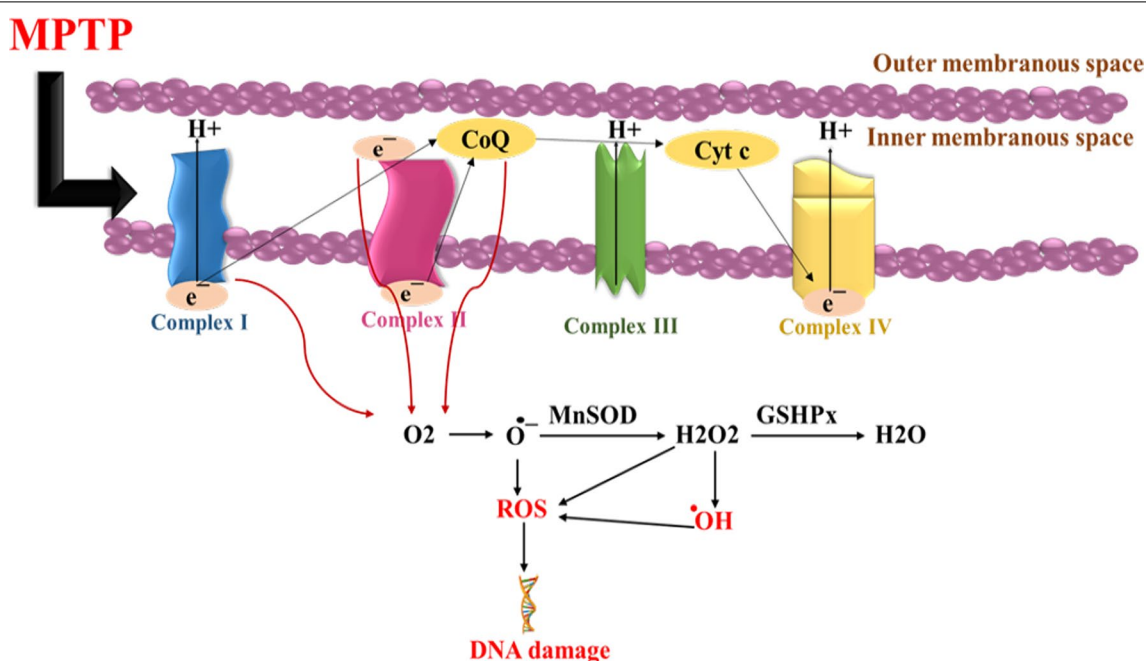

Fig. 1 The MPP + caused mitochondrial dysfunction. MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; CoQ, Coenzyme Q10; Cyt c, cytochrome complex; e^-, electron; O2, oxygen; O^-, singlet oxygen; MnSOD, manganese superoxide dismutase; GSHPx, glutathione peroxidase

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are also formed. The reactive oxygen species easily react with the DNA, proteins, and lipids, resulting in oxidative damage [15, 16]. Complex I activity is diminished in the platelets, skeletal muscles, and substantia nigra of Parkinson's disease patients [17].

Complex I abnormalities, as well as other flaws, play a key part in the death of dopaminergic neurons. Complex I structural alterations caused by a lack of apoptosis-inducing factors do not result in neurodegeneration due to dopaminergic cell death, but they do make dopaminergic neurons more vulnerable to neurotoxins [18].

Genetic mutations implication in mitochondrial dysfunction

Specific gene aberrations that trigger dopaminergic apoptosis have aided the mitochondrion's function in the progression and pathogenesis of Parkinson's disease. In familial PD, pathogenic mutations in Parkin, PTEN-induced kinase1, α-synuclein, DJ-1, LRRK2, UCHL-1, vacuolar protein sorting 35, and HtrA2 support mitochondrial dysfunction (Fig. 2) [19, 20].

SNCA (α-synuclein)

α-Synuclein (α-Syn) is a 140-amino acid polypeptide encoded by α-synuclein. The principal component of Lewy bodies, α-Syn, was originally linked to Parkinson's disease, and SNCA was later found as the first hereditary familial Parkinson's disease gene [21]. Increased

levels of the wild form of α-syn generate fragmentation in the mitochondrion and the generation of ROS. The mitochondrial and endoplasmic reticulum dissociate when mutant or wild-type α-syn is overworked, decreasing mitochondrial energy output and limiting Ca2+exchange [22].

Parkin

Parkin is a cytosolic E3 ubiquitin ligase that encodes for 465 amino acid cytosolic protein and also ubiquitinates target proteins. It regulates the production and death of mitochondria via mitophagy, which helps to keep them healthy. Parkin gene mutations have been reported as a factor of Parkinson's disease in autosomal recessive families [23, 24]. Parkin's proclivity for misfolding hints that it may be more prominent in the pathophysiology of sporadic PD. The development of non-native, non-functional parkin can be influenced by a variety of pathogenic mutations as well as high oxidative stress. The substantia nigra of sporadic PD patients has misfolded parkin [25–28].

PINK1

PINK (PTEN-induced putative kinase 1), a protein with a mitochondrial targeting sequence is encoded by this gene. PINK1 mutations are the second leading cause of autosomal recessive early-onset PD [29]. In autosomal recessive PD, various homozygous mutations have been identified in family PD patients. Mutations in PINK1
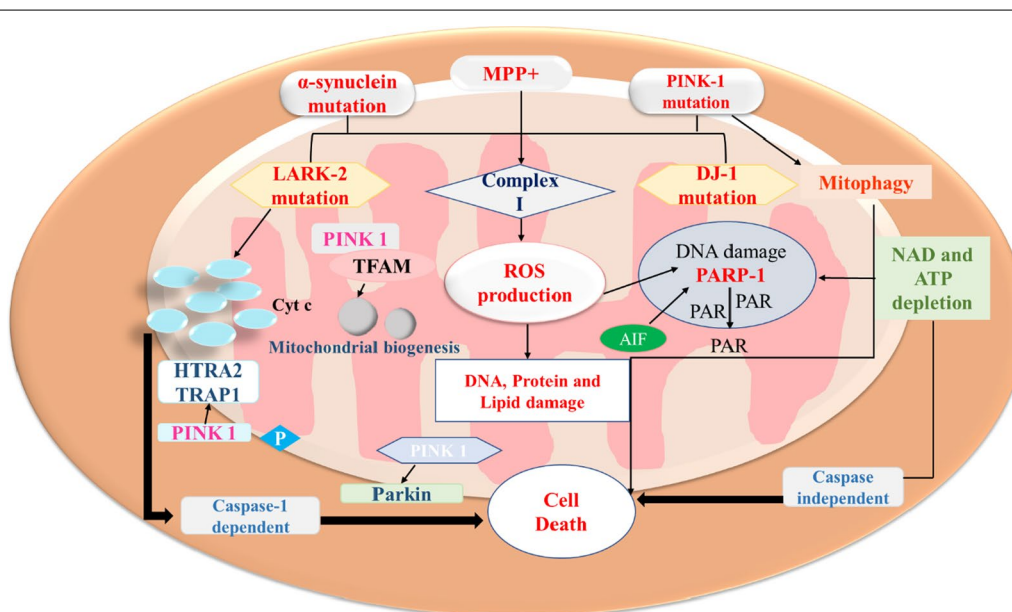

Fig. 2 Cell death pathways mediated by a mitochondrial malfunction in PD due to various compounds such as, α-synuclein mutation, and LRRK2, PINK1, and DJ1. Cyt c, cytochrome complex; TFAM, transcription factor A; HTRA2, high temperature requirement protein A2; TRAP1, tumor necrosis factor receptor-associated protein; AIF, apoptosis-inducing factor; NAD, Nicotinamide adenine dinucleotide; ATP, adenosine triphosphate; PAR1, polymerase-1

cause a decrease in ATP synthesis, a decrease in mitochondrial respiration, and an increase in the aggregation of an α-synuclein. Parkin translocates out from cytosol to the mitochondrion when the mitochondrial membrane potential drops. For mitochondrial localization, PINK1 needs mitochondrial translocase, and its phosphorylation of serines promotes Parkin migration, which leads to mitophagy. As a result, PINK1 dysfunction causes localization mistakes as well as impaired mitophagy [30].

LRRK2

Leucine-Rich Repeat Kinase 2 (LRRK2) is a multifunctional protein kinase. Its mutations induce an alternately penetrant autosomal dominant form of Parkinson's disease and are the most common cause of familial PD [31]. Increased LRRK2 activity leads to mitochondrial-dependent apoptosis, whereas LRRK2 deletion protects neurons from mitochondrial dysfunction [32]. Overexpression of wild-type or mutant LRRK2 with elevated kinase activity promotes mitochondrial fragmentation and dysfunction in multiple neurons, as well as increased ROS generation and H2O2 sensitivity [33–35].

Another process involves LRRK2 interacting with PRDX3 (peroxiredoxin 3), which is a mitochondrial member of the thioredoxin peroxidase antioxidant family. Phosphorylation of PRDX3 is enhanced by mutations in the LRRK2 kinase domain, resulting in increment of the ROS generation, reduction in the activity of peroxidase, and increased cell death [36].

DJ-1

DJ-1 is an anti-inflammatory, anti-apoptotic, and anti-oxidant neuroprotective protein. It accomplishes these health efficacies by acting as a transcriptional coactivator, as well as a ROS quencher [37, 38]. Variations in the DJ-1 gene are attributed to autosomal recessive, early-onset PD. Exhaustion of DJ-1 makes cells more vulnerable to oxidative stress. DJ-1 mutations do not safeguard against H2O2, 6-OHDA, H2O2, or MPTP whereas an excess wild-type DJ-1 does [39, 40].

Oxidative disbalance in Parkinson's disease

Oxidative disruptions have been considered a vital part of the progression of Parkinson's disease. When the volume of ROS produced exceeds the biological system's capability to destroy specific reactive intermediates, oxidative stress occurs, resulting in a harmful state that contributes to cellular damage. Numerous critical metabolic activities in the body create oxidative stress. Overproduction, on the other hand, has the potential to be detrimental to the body [41]. Approximately 20% of the body's oxygen supply is consumed by the brain, with a large percentage of that oxygen being converted to ROS. ROS can

arise from a wide range of regions in the brain. The electron transport chain serves as the primary source at the mitochondrial level in the production of ROS. Additional ROS sources include NADPH oxidase, monoamine oxidase (MAO), and other enzymes, as well as NO [42, 43]. ROS development can further destroy Complex I, resulting in both complex I damage and ROS formation.

The production of oxygen-reactive species harms the substantia nigra by protein peroxidation, DNA oxidation, and lipid peroxidation occurs in the pathogenesis of the PD. The main causes of this phenomenon are the changes in brain iron content, activation of MAO, mitochondrial dysfunction, and even changes in the antioxidant system [44–46].

Dopamine metabolism

Auto-oxidation of dopamine leads to the formation of free radicals and dopamine quinones. Enzymes such as catechol-o-methyltransferase and MAO are involved in dopamine metabolism [47].

Normally, MAO-A modulates dopamine levels through oxidative metabolism, which is predominantly found in catecholaminergic neurons [48]. In Parkinson's disease, however, when neurons die, MAO-B levels in glial cells rise, making it the predominant enzyme for dopamine metabolism [49, 50]. 3,4-dihydroxy phenyl-acetaldehyde, H2O2, and an ammonium molecule are the results of dopamine metabolism mediated by MAO-B. H2O2 interacts with Fe^{2+} in dopaminergic neurons to generate hydroxyl radicals [51, 52]. Transporting and storing DA increases the formation of ROS. The storage of dopamine necessitates transportation via the vesicular monoamine transporter 2. As a result, VMAT2 (Vesicular monoamine transporter 2) modulates cytoplasmic dopamine levels, minimizing the generation of ROS. Upregulation of VMAT2 guards against [53].

Excitotoxicity

Excitotoxicity is a pathogenic phenomenon in which glutamatergic receptors are overstimulated, causing neurons to be damaged and destroyed. Intracellular activities that elevate the oxidative burden and trigger apoptosis, such as calcium excess and bioenergetic changes, generate excitotoxicity. The bulk of excitatory signals are produced by glutamate [54]. If cellular ATP levels are low as a result of complex I failure, cellular homeostasis can be impaired. The $Na+/K+$ ATPase would be hindered if ATP was depleted, leading to considerable neuronal depolarization and a reduction in the voltage-dependent $Mg2+$ blocking of the NMDA (N-methyl-D-aspartate) glutamate receptor. In such environments, relatively minimal quantities of glutamate stimulation can induce excitotoxic NMDA receptor

stimulation and massive intracellular calcium transients. Due to energy deficit, insufficient mitochondrial calcium storage, and inadequate calcium ATPase activity may prolong or intensify these calcium transients. Reduced nigrostriatal dopaminergic input promotes overactivity of the subthalamic nucleus, which delivers excitatory glutamatergic projections to previously injured nigrostriatal neurons. As a result of the altered route, nigrostriatal neurons may be more vulnerable to excitotoxic shocks [55, 56].
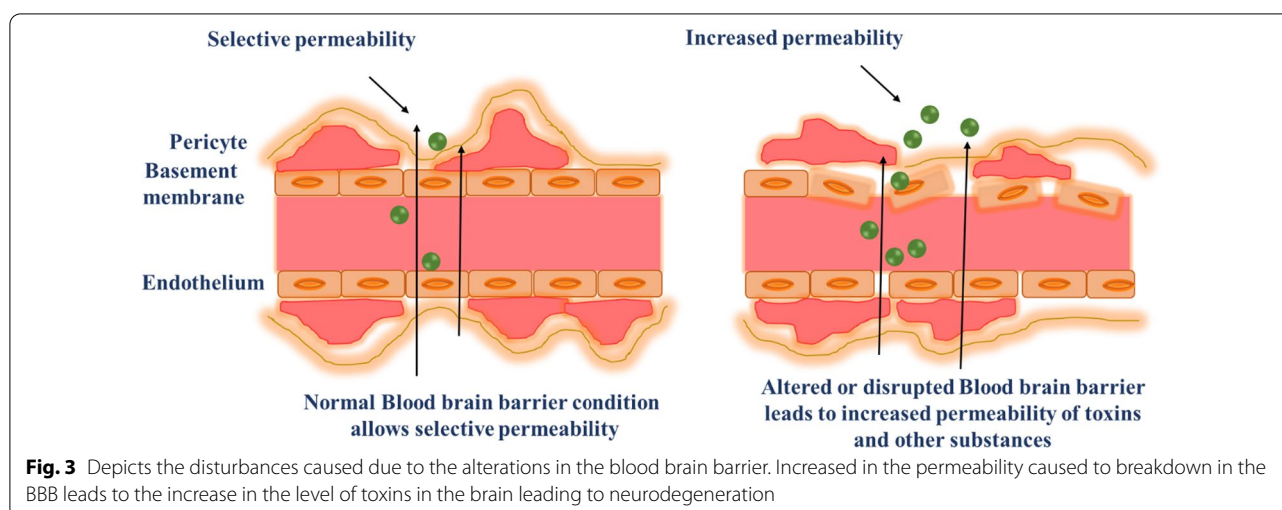
Lewy bodies

In Parkinson's disease, areas of neuronal loss are accompanied by the appearance of Lewy bodies. Lewy bodies are proteinaceous accumulations of neurofilaments, parkin, α-synuclein fibrils, proteasomal elements ubiquitin, ubiquitin carboxyl terminal, and hydrolase L1 (UCHL1) and a large number of proteins, most of which are likely unidentified. They are seen in the substantia nigra of PD patients [57]. The Lewy bodies are enormous intracytoplasmic inclusions with "halos'' and cores that lack a confining membrane. Structures are likely to be a little "sticky." The identification of α-synuclein mutations in familial PD and the evidence that Lewy bodies were highly immunoreactive in sporadic disease for wild-type α-synuclein as well as numerous other proteins in their normal or damaged forms renewed interest in Lewy bodies [58]. According to genetic variations attributed to familial PD, altered protein organization and/or disintegration could play a pivotal part in the progressive decline in sporadic PD. Defective protein breakdown has lately been identified as a key component in the degenerative process associated with Parkinson's disease [59].

Endoplasmic reticulum stress

Endoplasmic Reticulum (ER) stress has been found in body cells taken from Parkinson's disease individuals in a few studies. Increased expression of mutated α-Syn mimics stimulation of the unfolded protein response in cellular models of Parkinson's disease, resulting in chronic ER response to stress linked to neurodegeneration [60]. Furthermore, ER stress may respond to boost α-Syn agglomeration [61, 62], implying a chain reaction between ER stress and α-Syn aggregates. Kinetic studies have shown that the presence of toxic α-Syn oligomers at the ER correlates with the occurrence of ER stress and disease progression in mutant α-Syn transgenic mice. More importantly, α-Syn accumulation at the ER is also observed in post-mortem human brain tissue from PD patients [63].

Blood–brain barrier alterations

The blood–brain barrier (BBB) is a critical component of the neuronal interaction with the brain vascular system. The passage of ions, chemicals across brain cells and the circulation is strictly regulated by it [64]. The BBB is critical for separating neurotransmitters and neuroactive substances that govern the brain environment. The role of BBB alteration in Parkinson's disease has been heavily debated [65]. Clinical research has lately revealed evidence of BBB breakdown in Parkinson's disease patients. Blood–Brain Barrier breakdown has been observed in a variety of toxin-induced PD studies, notably 6-OHDA-treated rats and MPTP-treated rats [66] (Fig. 3). Parkinson's sufferers have a lower P-gap (glycoprotein) functioning in the center of the brain, which has been linked to a BBB breakdown [67, 68]. Notably, some studies have found that as people grow older, their BBB P-gap functioning decreases

Fig. 3 Depicts the disturbances caused due to the alterations in the blood brain barrier. Increased in the permeability caused to breakdown in the BBB leads to the increase in the level of toxins in the brain leading to neurodegeneration

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in numerous brain regions, indicating that they are more sensitive to the build-up of toxic chemicals in the brain. Given that α-synuclein deposition is linked to PD pathogenesis, it's conceivable that a decrease in P-gap is linked to an increase in α-synuclein levels in the brain [69]. However, more research is required to determine the role of the P-gap in this mechanism.

Mechanisms of apoptosis

Apoptosis is the primary cause of neuronal cell death in Parkinson's disease, as indicated by autopsy studies that found DNA segregation and apoptotic chromatin alterations in dopaminergic neurons of Parkinson's disease sufferers [70]. Furthermore, autopsy and in vitro investigations revealed significant growth of caspase-3 and higher expression of active caspase-3 in the substantia nigra, confirming the significance of apoptosis in the etiology of Parkinson's disease [71, 72]. Moreover, overproduction of anti-apoptotic proteins inhibits dopaminergic neurodegeneration in Parkinson's disease cell lines [73]. Caspase antagonists have also been demonstrated to prevent neurons from dying in Parkinson's disease cell lines, bolstering the theory that apoptosis is the primary cause of neuron loss in the condition.

Role of genetics in Parkinson's disease

While the precise pathological pathways causing dopaminergic neuron deterioration in the substantia nigra and clinical PD are unknown, it has long been established that PD runs in families. In keeping with this discovery, genetic analysis over the last two decades has demonstrated that DNA sequence variants do have a role in the disease's progression [74–76]. Five "causal" genes namely, SNCA, PINK1, LRRK2, PARK2 and PARK7 (DJ-1) that are involved in the disease's progression have

been uncovered through investigation over the previous decade. These genes have been identified as potentially damaging in PD because they are responsible for dysregulation of multiple physiological mechanisms (e.g., kinase signaling, mitochondrial respiratory chain function, ubiquitin-mediated protein degradation) [24, 77, 78].

PARK 1–10 are the ten monogenic variants of Parkinson's disease that have been identified, with genes identified in five of them. They come in two forms: autosomal dominant and autosomal recessive. The autosomal dominant form can only be found in a minority of families. Causative mutations in PARK1/PARK4 and PARK8 are linked to autosomal-dominant illness. The autosomal recessives, especially PARK2, are substantially more common, albeit they are still uncommon. PARK2, PARK6, and PARK7 are all autosomal-recessive genes. Even though these gene mutations are all very uncommon in the overall PD population, they are likely to be responsible for a significant part of early-onset PD (Table 1).

PARK1, which is linked to the A53T causal mutation in the α-synuclein gene. The α-synuclein protein is a critical feature of Lewy bodies in both sporadic PD and PARK1 sufferers. The A53T mutation causes levodopa-responsive parkinsonism that emerges early in life, lasts longer, and has a reduced tremor recurrence [79].

PARK2 (parkin), although there is a gradual loss of SN neurons, PARK2, the parkin gene, is inherited as an autosomal recessive illness with no Lewy bodies. PARK2 mutations have been found in people over the age of 50, indicating that it is not limited to young-onset PD. Parkin mutations are currently the most prevalent genetic cause of early-onset Parkinson's disease. Parkin has been discovered as a ubiquitin E3 ligase 61,62 that binds short ubiquitin peptide chains to proteins, likely to target them for breakdown via the ubiquitin/proteasome pathway [21, 80, 81].

Table 1 Summarizes the list of genes and their details associated with the PARK loci in Parkinson's disease [86, 87]

S. nos.	Name	Chromosome	Gene	Inheritance	Protein name	Mutation
1.	PARK 1	4q21-q22	α-Synuclein	Autosomal dominant	α-Synuclein	Lewy body and protein aggregation
2.	PARK 2	6q25.2-q27	Parkin	Autosomal recessive	Parkin E3 ligase	Cause functional mutation
3.	PARK 3	2p13	–	Autosomal dominant	–	–
4.	PARK 4	4q	Copies of α-synuclein	Autosomal dominant	–	Triplications of chromosomal Region that contains wild-type α-synuclein gene
5.	PARK 5	4p14	Ubiquitin C-terminal hydrolase L1	Autosomal dominant	9ubiquitin-carboxyl-terminal-hydrolase L	–
6.	PARK 6	1p35-p36	–	Autosomal recessive	PINK1 protein kinase	–
7.	PARK 7	1p36	DJ-1	Autosomal recessive	DJ-1	–
8.	PARK 8	12p11.2-q13.1	–	Autosomal dominant	Dardarin	–

PARK4 is triggered by the triplication of regions on chromosome 4 that comprise the α-synuclein gene and 17 other putative genes. Rather than being a distinct gene, PARK4 is an allelic variant of PARK1 [82]. PARK5, also abbreviated as UCHL1 (9 ubiquitin-carboxyl-terminal-hydrolase L), is a heterozygous I93M mutation that is autosomal dominant. UCH-L1 may serve a function in the ubiquitin–proteasome mechanism, and parkin mutations have been associated with Parkinson's disease. The ubiquitin-protein ligase UCH-L1 can act as a ubiquitin-protein ligase [83].

PARK6 (PINK1), the PARK6 gene was first discovered on chromosome 1p35–36. Two homozygous mutations in the phosphatase and tensin PINK1 gene were discovered during gene analysis. A decrease in ATP synthesis, a decrease in mitochondrial respiration, and an increase in the aggregation of an α-synuclein are all caused by PINK1 mutations. The putative protein kinase domain is affected by both of the first known PINK1 mutations: W437OPA defragments the final 145 amino acids of the C-terminus, while G309D alters a highly conserved amino acid position [84].

Another early-onset autosomal recessive mutation, PARK7, the DJ-1 gene, is characterized by modest progression and high sensitivity to levodopa. DJ-1 The oxidation of a cysteine residue has been postulated to cause DJ-1 to migrate to mitochondrial outer membranes and confer antioxidant action by direct free radical scavenging. Cells with cysteine residue mutations that prevent oxidation are also more sensitive to mitochondrial injury [29, 29]. PARK8 (LRRK2) is an autosomal dominant form of Parkinson's that was initially connected to the 12p11.2–q13.1 chromosomes. LRRK2 mutations are frequently linked to the later onset of PD. Pathogenic mutations in the new LRRK2 gene have been discovered, indicating that PARK8 is a key locus for PD, causing far more disease than PARK1 [85].

Symptoms associated with Parkinson's disease

While the clinical syndrome of Parkinson's disease was initially attributed to dysfunction of the basal ganglia, various research and findings have revealed that nondopaminergic neurons in other brain (such as the raphe nuclei, vagus dorsal motor nucleus, and locus coeruleus) play a significant role [88]. It is now well known that nondopaminergic pathways play a role in the progression of PD, as evidenced by the rising recognition of non-motor symptoms that have a negative influence on patients' quality of life [89, 90]. Henceforth, the symptoms are divided into two categories namely, motor symptoms and non-motor symptoms together which increase the complexity of the disease and also contribute to the discomfort to the patient.

Table 2 Motor symptoms associated with Parkinson's disease [91]

S. nos.	Motor symptoms
1.	Bradykinesia
2.	Muscular rigidity
3.	Postural instability
4.	Tremor
5.	Hypomimia (expressionless face)
6.	Speech disturbance
7.	Sialorrhea
8.	Dystonia
9.	Scoliosis
10.	Dysphagia

The depletion of dopaminergic neurons is the chief reason for motor complaints. It is estimated that nearly 80% of dopaminergic cells in the nigrostriatal pathway are disrupted before the cardinal motor characteristics of PD manifest. The following is a list of the most well-known and noteworthy motor symptoms (Table 2).

Non-motor symptoms, such as rapid eye movement disorder, olfactory problems, depression and constipation, are associated with increasing age and disease severity, though some non-motor symptoms, can appear early in the disease. The non-motor symptom complex's involvement and impact on the disease's progression. Even more than motor issues, non-motor symptoms can harm one's quality of life. Sensory dysfunction, sleep disorders, cognitive and mental disturbances, are all non-motor symptoms (Table 3).

Behavioral complications associated with Parkinson's disease and its medication
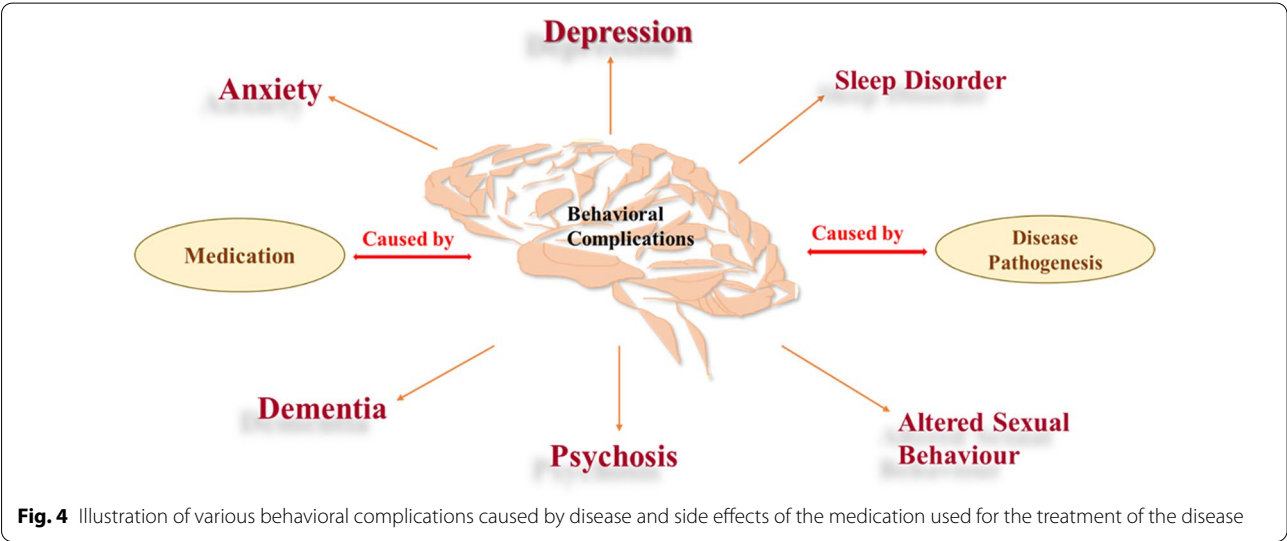
Parkinson's disease is predominantly a motor disease, although neuropsychiatric problems such as mood and anxiety disorders, lethargy, apathy, psychosis, cognitive impairment, dementia, sleep disturbances, and addictions frequently exacerbate the illness's progression. It might be caused by complicated interactions between the illness's gradual and broad pathologic changes, emotional reactions to Parkinsonism, and treatment-related adverse effects, or it can be caused by the disease itself (Fig. 4). Complications of the nervous system are prevalent [93]. Current knowledge on behavioral side effects of anti-parkinsonism therapy is summarized further in this article.

Depression in Parkinson's disease

One of the most prominent psychological issues mentioned by Parkinson's disease sufferers is depression. Despite this, it is usually overlooked. Depression affects 20–35% of those living with Parkinson's disease. From

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Table 3 Categories and prevalent non-motor symptoms of PD [92]

S. nos.		Non-motor symptoms	
1.	Autonomic Disturbance	Dizziness Visual disturbances Impaired cognition	Bladder disturbances Urgency Nocturia
2.	Neuropsychiatric disturbance	Depression Anxiety Anhedonia Hallucination	Illusion Delusions Dementia Delirium
3.	Sensory Disturbance	Pain Paraesthesia	Akathisia Olfactory disturbance
4.	Sleep Disturbance	Rapid eye movement Excessive daytime somnolence Vivid dreaming	Restless legs and periodic limb movements Insomnia Sleep disordered breathing
5.	Others	Fatigue Diplopia	Seborrhoea Weight loss

Fig. 4 Illustration of various behavioral complications caused by disease and side effects of the medication used for the treatment of the disease

the premotor to the late stages of the disease, it might hit at any time [94, 95]. Depression does not appear to be a straightforward reaction to the degree of physical impairment in Parkinson's disease, even though it has been postulated as a natural consequence of a worsening neurodegenerative illness [96].

The majority of Parkinson's disease patients report mild-to-moderate depression, with serious depression occurring less frequently. A complicated collection of neurotransmitters (mostly dopamine, serotonin, and norepinephrine) abnormalities is thought to be the origin of depressive illness in Parkinson's disease. It has been suggested that an allelic difference in serotonin transporters predisposes to mood disorders [97]. The following are the diagnostic criteria for major depression: persistent

and widespread negative moods, loss of interest and delight, as well as a spectrum of cognitive and physical symptoms. Optimizing dopaminergic medication for improved motor symptoms is key to managing depression in Parkinson's disease. Furthermore, levodopa, dopamine agonists, and selegiline have been examined as mild antidepressants and are thought to have modest antidepressant effects. Although additional research is needed, counseling, psychotherapy, and psychosocial support are also beneficial [98–100].

Psychosis
As early PD symptoms, psychosis emerges as transient hallucination and illusion. Based on their phenomenological properties, psychotic disorders can be categorized

into two kinds. Visual illusions or hallucinations harm only one set of people, whereas auditory and other hallucinations can occur infrequently. Delusions include guilt, envy, and robbery, to name a few [101]. Visual hallucination has a prevalence of 22–38%, while aural hallucination has a prevalence of 0 to 22%. Psychosis affects anywhere from 26 to 82.7% of the population. The existence of a Lewy body in the amygdala, a drop in the levels of dopamine in the retina, and a huge portion of amyloid parietal, and hippocampus areas are some of the essential pathophysiologic mechanisms of psychosis in Parkinson's disease sufferers [96].

Around 30% of people on long-term dopaminergic treatment develop psychosis as a result of their medication. When it comes to treating psychosis in Parkinson's disease patients, decreasing their PD medication is often the first step. In persons with Parkinson's disease, dopaminergic treatment has been attributed to the emergence of psychosis. If PD psychosis does not improve when the dose of PD drug is reduced, atypical antipsychotics are frequently considered [102]. Risperidone and olanzapine have been proven to aggravate Parkinson's disease; hence they are not encouraged. Consultation with a specialist is advised.

Anxiety

Anxiety is underrecognized and undertreated in PD patients due to clinical inaccuracy, symptom overlap with motor and cognitive elements of the disease, and diagnosis difficulty. Anxiety disorders are extremely prominent in Parkinson's disease patients, with rates ranging from 19.8 to 67% [103]. Anxiety symptoms may be caused by degeneration of subcortical nuclei and ascending dopamine pathways, along with norepinephrine and serotonin channels inside the frontal–basal ganglia circuits [104]. Panic disorder, generalized anxiety disorder, and social phobia are the most frequent anxiety disorders in people with Parkinson's disease. The biggest predictors of low quality of life are anxiety and depression. They can appear before the beginning of motor symptoms or in the latter stages of Parkinson's disease. Selective serotonin reuptake inhibitors, buspirone, and benzodiazepines are the most common pharmacological therapies. Cognitive-behavioral therapy, for example, is a nonpharmacological treatment approach.

Dementia and cognitive impairment

Dementia is widespread with Parkinson's disease, especially in its later stages. Modest cognitive impairment of PD is a term used to signify mild cognitive impairment in people with PD who do not have dementia. Cognitive impairment linked with idiopathic PD can take years to manifest and may be caused by the disease's pathogenesis [105–107]. Patients with Parkinson's disease and dementia (PDD) are more likely to experience neuropsychiatric symptoms. There is currently no defined diagnosis for dementia in Parkinson's disease. Dementia in Parkinson's disease appears as a mix of subcortical and cortical dementia. The slowness of the mind, decreased working memory, executive dysfunction, and deficiencies are all subcortical characteristics. Memory impairment and language dysfunction are two cortical traits.

Dementia can be triggered by Lewy body syndrome in the posterior cortical areas. The loss of dopamine transporters in the striatum, as well as aging and a decrease in cortical cholinergic markers, all promote the dementing cycle in Parkinson's disease [108]. After all other causes of dementia have been ruled out, the definitive diagnosis of dementia caused by Parkinson's disease must be confirmed. Treatments for PDD are mostly symptomatic. The parts of cognitive impairment that are exacerbating should be removed first (dehydration, metabolic factors). Additionally, any non-essential medications (e.g., anticholinergic or sedative drugs) should be stopped. Studies have looked at the efficacy of donepezil, galantamine, rivastigmine, and memantine as treatments. Only rivastigmine has been proven to be effective in dementia linked with Parkinson's disease [109, 110].

Altered sexual behavior

In Parkinson's disease patients, sexual interest revival is a well-known side effect of dopaminergic medication. Increased sexual function frequently entails a return to regular sexual activity as well as improved motor function. Hypersexuality, on the other hand, is a topic that has received less attention. Although the exact cause of this obsessive behavior is obscure, it could be linked to either increased sexual drive or a lack of sexual impulse control. Both rely on dopaminergic regulation. As the drug dosage is dropped, the sexual changes generally drift away [111, 112].

Sleep disorder

Sleep disturbances are prevalent in people with Parkinson's disease, and they can be caused by the disease, drugs, or comorbidities (pain, mood disorders, and cognitive impairment). Sleep disturbance has a severely detrimental effect on their quality of life. Daytime symptoms, overnight sleep disturbance, sleep-related movement disorders, and parasomnias are all common sleep issues in people with Parkinson's disease. Difficulty getting asleep, inability to maintain sleep, and excessive daytime sleepiness are all examples of sleep disorders. The motor issues that PD patients acquire, such as bradykinesia, stiffness, and rest tremor, may make it difficult to fall asleep or stay asleep [113].

Insomnia is defined as a state of weariness caused by a perception of inadequate or poor-quality sleep. Issues with going back to sleep, sleep fragmentation, and waking up early in the morning are all part of it. A multitude of circumstances might obstruct the onset and preservation of sleep.

Insomnia is frequently caused by motor signs of Parkinson's disease (stiffness, tremor, inability to move in bed, and dystonic movements) and nocturia. Other sleep disorders, such as restless legs syndrome, periodic limb movement disorder, and obstructive sleep apnea syndrome, as well as certain drugs, have been reported to disrupt regular sleep [114]. Hypersomnia is a condition characterized by excessive daily weariness and sleep episodes. Excessive daytime sleepiness in Parkinson's disease can be influenced by a series of factors, including difficulty sleeping at night, progression of the disease, the influence of dopaminergic and other pharmaceuticals, and comorbid disorders such as depression or dementia. All dopamine agonists, as well as levodopa alone, have been linked to sleep attacks [115].

The term "parasomnia" refers to indications and symptoms that occur during sleep. Many patients with Parkinson's disease report vivid dreams, panic attacks, nightmares, nocturnal vocalizations, sleepwalking, sleep talking, and rapid eye movement. Changing PD drugs to improve mobility or lessen dyskinesias could be enough to enhance sleep.

Conclusions

Parkinson's disease is a neurological disorder that affects adults and is distinguished by the depletion of nigrostriatal dopaminergic neurons. A condition wherein the brain does not make adequate dopamine is known as dopamine inadequacy. Parkinson's disease has a clear link to mitochondrial malfunction and oxidative stress in its etiology. Identifying treatments that directly address the disease processes underlying PD or prevent the spread of disease onset is crucial, as only symptomatic medications are presently accessible. In Parkinson's disease, α-synuclein is linked to mitochondria and LRRK2. In PD brains and cell models, LRRK2 combines with α-synuclein. Parkin and PINK1 are engaged in mitophagy, and DJ-1 is vital in reducing oxidative stress-induced toxicity within the mitochondria. In Parkinson's disease, mutations in these genes induce mitochondrial malfunction, which leads to neurodegeneration. Despite growing awareness that mental symptoms are integral to Parkinson's disease and can have a substantial impact on functional ability, many questions about the optimal treatment options for all of these conditions remain unanswered. Better treatments for the neuropsychiatric consequences of Parkinson's disease will be required to reduce the disease's burden on patients and their relatives.

Declarations

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