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# A REVIEW ON THE MITOCHONDRIAL DYSFUNCTION IN SPORADIC PARKINSON'S DISEASE

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**ABSTRACT:** Parkinson's disease is the second most common progressive, age-linked neurodegenerative disorder. The sporadic form of the disease is usually idiopathic, where mitochondrial dysfunction is its major hallmark. Mitochondria are multifunctional dynamic organelles that carry out major cellular functions that get damaged by reactive oxygen species, deposition of lewy bodies, dopaminergic neuronal cell death, mitochondrial DNA mutations, and imbalance in fission/fusion that ultimately weakens mitophagy. In this review, the updated key roles and mechanisms of mitochondrial dysfunction structurally and functionally in the pathogenesis of sporadic Parkinson's disease are discussed to understand the process of neurodegeneration. Research Data from numerous studies confirm mitochondrial dysfunction being the Basis of the disease. Here, we briefly bring the overview of illicit drug administration, oxidative stress, mitochondrial DNA mutations, mitochondrial genome mutations, alpha-synuclein aggregation, mitochondrial dynamics-fission and fusion, and the impairment of mitophagy in the disease pathogenesis. In conclusion, understanding mitochondrial dysfunction and its pathways can be a major target in treatment and prevention of Parkinson's disease.

**INTRODUCTION:** Parkinson's disease (PD) was first started in an essay on "shaking palsy" by James Parkinson in 1817. In the beginning, it was discussed as "paralysis agitans" but Later was acknowledged as "maladie de Parkinson" or simply Parkinson's disease by Charcot in 19th century [1]. It has approximately 3-7% of lifetime risk after Alzheimer's disease and is an age-linked progressive condition that is expected to increase exponentially in the elderly population.

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Universally about 2.5 to 6.1 million patients have been afflicted with PD since 1990 to 2016 [2]. A report by Lau and Breteler presented in 2006 projected 10 Million individuals, *i.e.,* almost 0.3% of the global population suffered from PD amongst which 1% were beyond 60 years.

In India, the precise reports about the pervasiveness of PD are known only in limited population-based studies [3]. The incidence of PD in men is twice more common than in women; this prevalence may be due to differences in variables like postmenopausal hormones, caffeine intake, and cigarette smoking behavior. A study confirmed by the global burden of disease suggests that the number of PD cases will be doubled by 2040, signifying a 'PD pandemic' probably [4]. In accordance with US Census Bureau population projection, there will be

an approximate rise of 1,238,000 PD patients by 2030 [5]. Regardless of the ideal treatments, intense disabilities are observed in the later stages of PD as the time progresses. PD is idiopathic, and a highly common chronic, multifactorial, neuro-deteriorating disorder, characterized primarily by the degradation of dopaminergic cells in substantia nigra pars compacta (SNPc) and extensive accumulation of an intracellular protein called alpha-synuclein. Despite ideal medical and surgical treatments available for PD, there is the absence of a convinced treatment worsening the condition leading to extreme debilities [6, 7]. This is the result of deficiency of dopamine, funding the presence of motor and non-motor features. The non-motor clinical outcomes comprise sensory impairments like depression, tingling and pain, hyposmia, and altered cognitive functions, whereas the primary motor manifestations include resting tremors, rigidity, bradykinesia, postural instability, and gait disturbances [8]. The sporadic disease is a condition arising in a population unsystematically with an unknown cause [9]. Various neurotoxins like heavy metals, synthetic components, and sometimes dopamine itself are believed to be environmental risk factors. The risk factor of PD is usually unidentified; however, numerous risk factors for sporadic PD consist of toxin, contact with pesticides, oophorectomy, positive family history, and most importantly advancement in age. The genome-wide mutational and genetic studies carried out recently provide data about different genetic risk factors. Microglial activation in damaged areas participates in advancing disease as a local micro-environmental factor [10, 11]. Early-onset PD are seldom inherited, amongst which few are linked to specific gene mutations. Pathologically PD is also named as 'mitochondrial disease of senescence'. The depletion of dopaminergic neurons in PD is due to the deformed genes like DJ-1, PINK1, LRRK2 that distresses mitophagy, damaging mitochondrial respiratory chain and releasing Reactive oxygen species (ROS) in the brain, accompanied by mitochondrial dysfunction, dopaminergic neuronal death, and atypical protein accumulation [12] that is interlinked with each other as shown in **Fig. 1** [13].

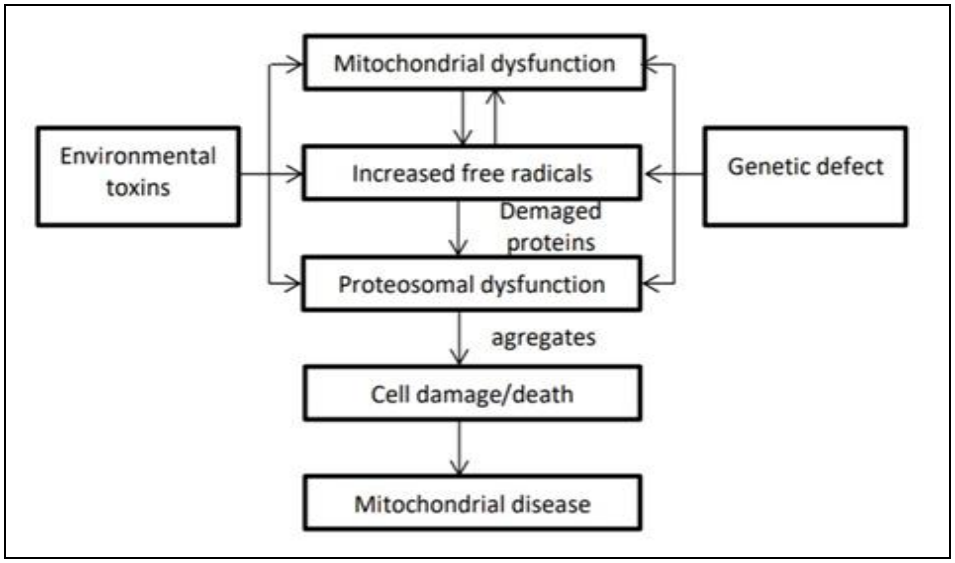


**FIG. 1: POTENTIAL LINK AMONG ENVIRONMENTAL AND GENETIC FACTORS AND MITOCHONDRIAL DISEASE**

**Pathogenesis of PD:** The principal concept in the pathology of PD is the depletion of cells within substantia nigra, which specifically affects the ventral component of pars compacta resulting in impairment of basal ganglia circuitry. The neurochemical changes in PD originate within the striatum and other nuclei in the basal ganglia. At the time of death, about 70% of dopaminergic degeneration in PD patients was reported when compared to normal individuals [14, 15]. Abnormal intracellular protein aggregates such as Alpha-synuclein immunoreactive inclusions and ubiquitin get settled as Lewy bodies. The pathogenic pathway of Lewy bodies initiates from cholinergic and mono-aminergic neurons in the brain stem followed by the olfactory system; however, the limbic and neocortical regions of the brain come along as the disease progresses.

The death of dopaminergic neurons that was first destined to SNPc becomes extensive at the last phase when the disease gets finally established [16, 17]. Numerous theories have been explained about the pathogenesis of PD, were as in idiopathic PD, alpha-synuclein is considered as the chief constituent in the lewy bodies and lewy neuritis. The process of production of lewy bodies is confirmed by scientists as subordinate to the refractive proteolytic pathway that causes an unusual breakdown or increased production subjected to genetic mutations. It is confirmed that alpha-synuclein modifies dopamine biosynthesis and negatively controls the dopamine transporter system [18, 19]. Apart from the mechanisms mentioned above, other various routes are expected to be involved. Several studies have put forward about the abnormal protein clearance, mitochondrial dysfunctioning, and neuroinflammation giving information about the commencement and advancement of PD. Nevertheless, the connection amongst these pathways remains vague [20].

The updated studies on PD report indicated that mitochondrial dysfunction and oxidative stress are the primary PD mechanisms. The complex 1 deficiency understood as the uninterrupted relation between mitochondrial dysfunction and PD in SNPc; this deficiency was also successively observed in skeletal muscles and platelets. DA neurons being more susceptible to oxidative stress resulted in the association of auto-oxidation and DA metabolism, a rise in iron and a fall in total glutathione levels was seen along with mitochondrial complex 1 inhibition that led to surpassing the oxidative capability of DA cells, eventually causing cell death [18].

**Mitochondrial Dysfunction (MD):** Mitochondrial vulnerability to age-linked oxidative stress makes mitochondrial dysfunction a highly common cause for neuro-depletion. The proof of mitochondrial dysfunction is revealed from mitochondrial toxin-induced models and observations of mitochondrial deformities in the postmortem tissues from patients with idiopathic PD. Mutations in genes linked with the disease encoding for proteins responsible for normal mitochondrial functions have also been identified. Furthermore, concluding that mitochondrial dysfunction is a hallmark of PD [21].

An enormous number of PD cases are idiopathic, however certain exogenous factors and particular genetic mutations are known to cause sporadic PD and chiefly mitochondrial complex I dysfunctioning in specific is linked to it; similarly, a study on postmortem tissues of PD patients confirms that the free radicle hypothesis is acquainted with the latter resulting in free radical injury and impairment in an enriched release of ROS that consecutively damages normal mitochondrial functions in vicious cycle [22, 23].

Mutation in parkin (CHCHD2) within the fibroblast decreases the process of Oxidative phosphorylation in complex I and IV, resulting in the breakdown of mitochondrial reticular structure. Also, a meta-analysis study reported the damage to complex I and IV in substantia nigra, cerebellum, peripheral blood, and the central cortex. The number of mitochondria were observed to be inversely proportional per cell (resulting in a fall in the number of mitochondria per cell) [24].

These dynamic, systematically structured double-membrane organelles are reputable to regulate apoptosis, maintain calcium homeostasis, and contribute to the synthesis of vital metabolites and ATP production [25]. Mitochondria relentlessly function by the process of fission and fusion. Mitofusions (MFN1) regulate the fusion of the outer mitochondrial membrane (OMM), whereas optic atrophy 1 controls fission that is destined to the inner mitochondrial membrane (IMM) [26]. The neurons are susceptible to fluctuations in mitochondrial function as numerous neuronal actions like ion channels, axonal/dendritic transport, synaptic transmission, and ion pump actions require a high amount of energy. Mitochondrial damage can severely effect neuronal function and survival. Hence, it is not shocking that any imbalance in mitochondrial fission or fusion weakens normal mitochondrial functions and incidence of neuronal diseases and is accompanied by mutations in mitochondrial fission and fusion genes, emphasizing the connection among the neuronal activity and mitochondrial dynamics [27].

Besides all, oxidative damage facilitates cellular pathology. Recent studies reveal that medium to low level of ROS participates incritical regulation of the pathways in cellular homeostasis. **Fig. 2** [28]

$H_2O_2$, hydrogen peroxide; $HO^{\bullet}$, hydroxyl radicle; $O_2^{\bullet-}$, superoxide anion radicle; GPx, glutathione peroxidase; GRed, glutathione reductase; GSH, Reduced glutathione; SOD, superoxide dismutase.

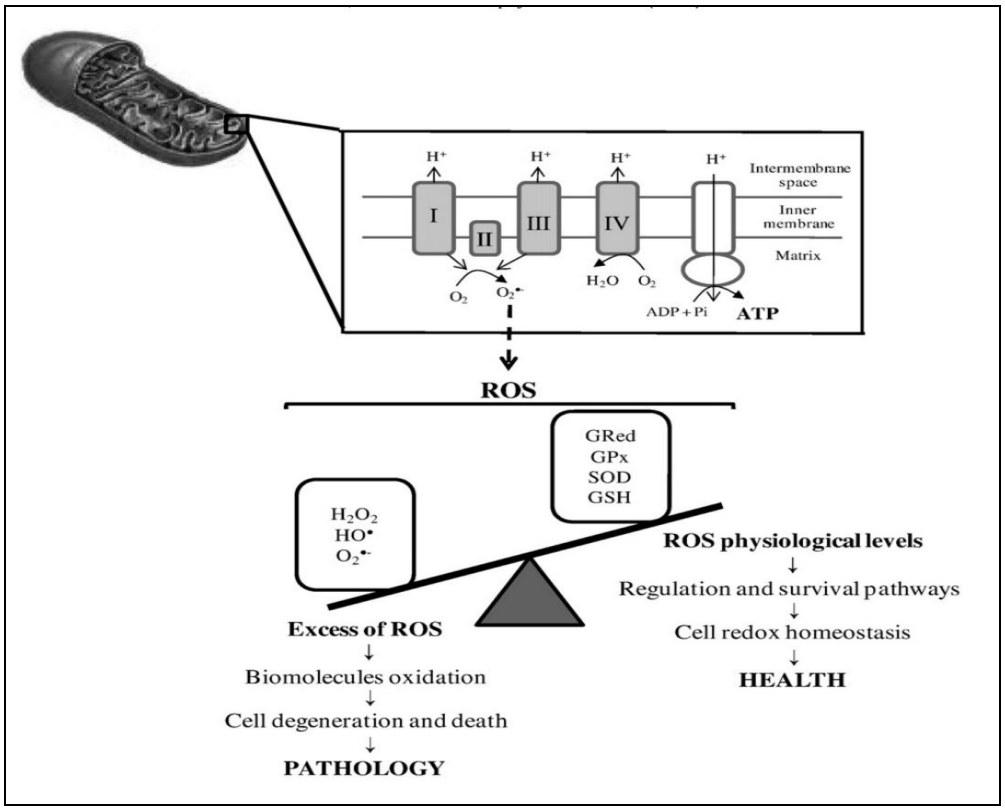


**FIG. 2: THE TWO FACES OF MITOCHONDRIA**

**Mitochondrial Dysfunction in Sporadic PD:**

**Illicit Drug Administration:** Mitochondrial dysfunction is strongly associated with PD, and this direct connection was reported by Langston *et al.* in 1983. Four patients within a week developed distinctive symptoms of Levodopa responsive Parkinsonism upon introducing what they had thought to be a 'synthetic heroine' intravenously.

Chemically it was a mitochondrial toxin 1 - methyl – 4 – phenyl - 1, 2, 3, 6-tetrahydropyridine (MPTP) [29]. In a little while, inhibitory and neurotoxic effects of MPTP were deep-rooted. Therefore, it is well established that the neurotoxicity of MPTP gets initiated by its toxic metabolite 1-methyl-4-phenyl-pyridinium ($MPP^+$). MPP+ is polar in nature. MPTP crosses the blood-brain barrier, where the enzyme mono-amino oxidase B (MAO-B) catalyzes it to form an intermediate MPDP+ that rapidly undergoes auto-oxidation from $MPP^+$ that selectively damages dopaminergic neurons and inhibits respiratory chain complexes I III and IV. Due to impaired respiratory chain, there happens to be oxidative stress, loss of bioenergetics functions, and diminished calcium homeostasis [30, 31]. Another mechanism is that $MPP^+$ that gets deposited in dopaminergic neurons in SNPc generates ROS along with superoxide anion ($O_2^-$), hydrogen peroxide ($H_2O_2$), Nitric Oxide (NO), and hydroxyl radicles (·OH). Apart from this, intensification of intracellular and extracellular dopamine auto-oxidation takes place that leads to the formation of cytotoxic quinolones [32].

**Oxidative Stress:** The brain utilizes a large amount of Oxygen, where a major amount gets transformed into ROS. The excessive production of ROS leads to oxidative stress in PD patients. Mitochondria is crucial for ROS production, mainly in complex I (nicotinamide adenine dinucleotide dehydrogenase) and complex III (cytochrome bc1) [33]. Neurotoxic components such as rotenone and $MPP^+$ inhibit the mitochondrial ETC complex I enzyme and NADH-ubiquinone oxidoreductase. It leads to electron leakage, where ROS gets released as the main byproducts during energy production. The tendency of ROS production and mitochondrial DNA (mtDNA) mutations rises with advancement in age, *i.e.*, more than 10-20 folds than in nuclear DNA. Mt DNA is effortlessly targeted by oxidation as it

is insecure due to the absence of histones [34]. The cellular free radicles that are commonly released are superoxide radicle ($O_2^{-\bullet}$), nitric oxide ($NO^{\bullet}$), and hydroxyl radicle ($OH^{\bullet}$) [30]. Hydrogen peroxide ($H_2O_2$) and peroxynitrite ($ONOO^-$)aren't free radicles but facilitate generating free radicles by chemical reactions. The DA cell death in SNPc proves this site is highly susceptible to Oxidative stress and lacks the protective mechanism. Following alterations in SNPc are found that are precisely in PD:

i. Formation of neuromelanin and increase in oxidation of dopamine.

ii. Increases in iron concentration and decrease of ferritin concentration.

iii. Decrease in production of reduced glutathione and increase in the level of oxidized glutathione [35].

The chronic inflammation associated with PD is regulated by the immune cells of the brain called microglia; due to certain exogenous and endogenous factors, it gets transferred to a hyperactive region and releases ROS resulting in neurotoxicity; apart from this the enzymes like NADPH oxidase (NOX2) gets deposited in microglia that destroy the remaining neurons by amplifying pro-inflammatory responses[36].

**Calcium Homeostasis:** Calcium ($Ca^{2+}$) is involved in numerous signaling pathways; the acceptance of $Ca^{2+}$by mitochondria is employed to buffer cystolic $Ca^{2+}$and safeguard from the increased $Ca^{2+}$ rushes. The Mitochondrial $Ca^{2+}$is highly necessary for typical physiological functions, as it positively controls the TCA cycle enzymes and constituents of the electron transport chain. A steep $Ca^{2+}$ dyshomeostasis is witnessed in neurodegenerative disorders [37]. The predisposed regions to PD in DA neurons may enforce an elevated demand for $Ca^{2+}$, making these neurons more susceptible to $Ca^{2+}$ dyshomeostasis associated with genes such as parkin and PINK1. Still, their mechanism of action remains unclear and is debatable [38]. The mitochondrial $Ca^{2+}$ efflux gets delayed intensely, leading to damage in $Na^+/Ca^{2+}$exchange in the mitochondrial $Ca^{2+}$ homeostasis; functionally, this defect makes mitochondria more susceptible to excess $Ca^{2+}$depolarizing the mitochondrial membrane instigating $Ca^{2+}$ dependent cell death. Various observations report about the pathophysiology of PD providing a connection between $Ca^{2+}$ models and mitochondrial Dysfunctioning [39].

It is also found that alpha-synuclein aggregation might be due to its engagement with the mechanism of $Ca^{2+}$ homeostasis. According to recent investigations, this phenomenon was linked to a rise in intramitochondrial Ca2+, increasing NO levels, releasing cytochrome c from mitochondria, and oxidative destruction, ultimately causing apoptosis [40].

**Mitochondrial DNA (mtDNA) Mutations:** mtDNA is the double-stranded circular genome that replicates independently. It is of about 16.6kb kilobyte that can encode 13 proteins i.e, seven subunits of complex I, one complex III subunit, three complex IV subunits, and two of ATP synthase. Additionally, mtDNA codes for 22 tRNAs (Transfer ribonucleic acid) and two rRNAs (ribosomal ribonucleic acid). Due to the lack of efficacy in DNA repair mechanisms and the Non-existence of histones, mtDNA is more susceptible to damage by ROS and mutations [41]. Though mtDNA sequencing does not disclose distinctive pathogenic mutation, an age-related rise in mtDNA deletion related to respiratory chain dysfunctioning was identified in SNPc [42]. It is nearly impossible to determine the effects of these deletions on bioenergetic activities; nevertheless, the reduced histochemical activity of an enzyme Cytochrome-c oxidase was observed in PD patients due to increased mtDNA deletions. Therefore, mtDNA tends to aggregate in DA cells in SNPc.These deletions extensively lead to mitochondrial dysfunction and neuropathy [43].

From the maximum number of recorded studies, it is found that respiratory chain-deficient muscle fibers tend to have a greater level of mtDNA deletions when compared to normal fibers; it has also been confirmed that complex I defects can probably be shifted to mitochondrial deficient platelet cybrids that result in altered calcium homeostasis due to damaged mitochondrial membrane potential, decreased ATP production and uplifted ROS formation [44]. Apart from this, mtDNA can undergo region-specific mutations to

organize the haplogroups phylogenetically. Therefore, these geographically-dependent mutations have revealed few significances that influence PD manifestation [45]. However, mtDNA mutations in sporadic PD are still a field of investigation. Even though numerous single polynucleotide polymorphisms have been confirmed more frequently in PD patients, neither could reliably explain the concept [46].

**Mitochondrial Genome Mutations:** Sporadic PD are basically non-genetic, but 5-10% are currently known to originate as monogenic forms of PD. The Autosomal recessive as well as dominant forms of PD are supplemented by 9 genes and 13 loci. Mutations in the SNCA genes *i.e.* PARK1 is exceptionally seen, were as the overexpression of PARK4 leads to toxicity [47]. Similarly, mutations in a multi-domain protein LRRK2, responsible for encoding 2527 amino acids, form 3.6% of sporadic PD cases 48 and more often get substituted by G2019S pathologically. Numerous studies have depicted a link amongst specific haplotypes within SNCA locus and sporadic PD; its duplicates are often observed, resulting in increased vulnerability to PD upon SNCA alterations. Moreover, the casein kinase-1 (CK1) or cyclin-dependent kinase-5 (Cdk5) responsible for serine phosphorylation endorses the impairment of parkin (PARK2) functions that facilitate the pathogenesis of sporadic PD [49]. Parkin locus undergoes a higher degree of mutation; this might be because it is situated inside FRAGE6, a common fragile site [50]. Likewise, the PINK1 mutations on 1p35-36 (PARK6) lead to autosomal recessive PD and comprise 1-4% of sporadic PD cases [51]. The mutation in DJ-1(PARK7) is usually uncommon, and their pathway in sporadic is yet to be understood; however, it is evident that this redox-related protein parallelly acts in the oxidative stress hypothesis [52].

**Alpha-synuclein in Mitochondrial Dysfunction:** Alpha-synuclein aggregation is a pathogenic hallmark in PD; as a result of oxidation or phosphorylation, it starts depositing as lewy bodies and impairs various other metabolic pathways leading to neuronal cell death. Impairment of complex I in sporadic PD due to alpha-synuclein is an extreme topic of investigation [53]. The misfolded or disordered alpha-synuclein monomers form beta-sheet-rich oligomers involving protofibrils of heterogeneous arrangements comprising spheres, chains, and rings, resulting in the formation of amyloid-like fibrils called: alpha-synuclein fibrils that ultimately precipitate forming lewy bodies [54]. The insoluble forms of alpha-synuclein-like fibrils and oligomers fashioned due to mutations and proteostasis are categorized as major types of Lewy bodies comprising tau, Huntington, and superoxide dismutase proteins [55].

Numerous studies have reported that oligomerization or over-expression of alpha-synuclein in mitochondria results in inhibition of mitochondrial complexes I II IV and V, elevated mitochondrial fragmentation, permeabilization of mitochondrial-like lipid vesicles and decrease in mitochondrial $Ca^{2+}$ retention [56] damages the trafficking and functioning among endoplasmic reticulum, Golgi apparatus, and the autophagy lysosomal system [57]. Apart from this, alpha-synuclein binds to OMM proteins like voltage-dependent anion selected channel 1 (VDAC1), translocase of outer membrane 40 (TOM), and Translocase of outer membrane 20 to facilitate MD [56]. Moreover, in sporadic PD, there was a decrease in VDAC1(voltage-dependent anionic selective channel-1) in the nigral neurons, essential for neurite maintenance and spinal cord protection by demyelination that is accompanied by alpha-synuclein accumulation and inclusively influences mitochondrial dysfunction [58].

**Mitochondrial Dynamics Mitochondrial Fission / Fusion:** Mitochondrial dynamics classically explain mitochondria's transportation to axon and dendrites, including the process of mitochondrial fission and fusion. In neurodegenerative conditions, these energy-dependent processes get disturbed, weakening the transportation, weakening synaptic functions. Likewise, for effective mitochondrial and neuronal functioning, well-adjusted fission and fusion are mandatory [59].

The fundamental action in the brain is neuronal signaling via electric impulses and chemical synapses. In PD, debility of synaptic terminals gets initiated over a long period, even before the first symptom is observed in the patient. Mitochondria is multifunctional; providing ATP to the neurons and buffering the cytosolic calcium are two major

functions that manage the electrochemical gradients and recycle and discharge the synaptic vesicle dependent on each other [60].

**Fission and Fusion:** Mitochondrial fusion and fission happen in a repeated cyclic manner usually. But, in the case of PD the normal course and morphology get affected. According to recent studies, there is a dependent and an independent impact on the fission/fusion proteins by alpha-synuclein; according to recent studies, these dealings feature in the pathological variants, oligomers, and fibrils that omits the negative influence on mitochondrial dynamics, as a normal characteristic of monomer [61]. Mitochondrial fusion is intervened by IMM regulated by GTPase (guanosine diphophatase) optic atrophy 1 (Opa1) and two mitofusions in the outer membrane. Genetic deficiency in Opa 1 cause's mitochondrial fragmentation, and overexpression encourages mitochondrial elongation [62]. The two GTPase homologues, mitofusin 1 (MFn1) and mitofusin 2 (mfn2) safeguard the OMM fusion, which are 80% sequentially alike in humans when compared to that of mammals. Overexpression of Mfn1 leads to mitochondrial disintegration, and that of Mfn2 causes swelling of mitochondria and additionally controls the mitochondrial-endoplasmic reticulum binding. Effective mitochondrial fusion enhances the resistance towards cell injuries, whereas any sort of mutation leads to genetic neuro-degeneration [63].

Mitochondrial fission relies on dynamin-related protein 1, mitochondrial fission factor (Mff), mitochondrial fission protein 1(fis1), and mitochondrial dynamics protein of 49kDa [64]. The Drp1 undergoes post-translational adaption depending on the type of isoform utilizing a small ubiquitin-like modifier (SUMO) that eventually affects the mitochondrial fission. SUMO2/3 resists Drp1-mff interactions stopping mitochondrial disintegration; conversely, SUMO-1 alleviates Drp1 facilitating fragmentation, which indicates the connection between SUMO and PD, associating mitochondrial dynamics in pathogenesis of PD [65]. Fission is related to cell death, which aids in carrying apoptosis. In addition, it helps in mitochondrial trafficking and cell division. The dominant-negative drp1 homologs decrease functional plasticity of synapse and mitochondrial content. Moreover, the dynamic changes in mitochondrial fission/fusion are a confirmation that autophagic-degradation plays a key role in amending neurite morphology mitochondrial content [66].

**Mitochondrial Mitophagy:** Lemasters entitled the word "mitophagy," which is a specialized lysosome-mediated degradation pathway [67]. It is the process of clearance of dysfunctional mitochondria for disintegration in autophagosomes by either mechanism, *i.e.*, mitochondrial receptor-dependent or independent. Mitophagy maintains mitochondrial homeostasis and is responsible for overall neuronal health; multiple studies have confirmed that impaired mitophagy leads to neuronal death, ultimately causing neuro-depletion. In PD patient's abnormal mitophagy was detected in both genetic and environmental forms [68]. Receptor-independent mitophagy includes re-defining of mitochondria when translocation of PINK1 from cystol to mitochondria takes place. The diminished mitochondrial membrane potential and obstructing PINK1-degrading proteases cause deposition of PINK1. As a result, mitophagy gets initiated by OMM proteins, eventually causing mitochondrial engulfment by autophagosomes. Over-expression of alpha-synuclein reduces LC3-positive vesicles in neuroblastoma cells [65]. It was also detected in the fibroblasts of patients with sporadic PD along with mitochondrial dysfunction and damaged mitophagy [69].

**CONCLUSION:** Mitochondrial dysfunction is an undebatable contributor to the pathogenesis and progression of sporadic Parkinson's disease and opens up a potent target for disease treatment. The environmental risk factors result in a cascade of impaired mitochondrial functions that trigger the pathogenesis of Parkinson's disease. The major consequences of mitochondrial dysfunction are deposition of alpha-synuclein, imbalanced calcium homeostasis, formation of reactive oxygen species, and ultimately damaging the mitochondrial dynamics. However, it remains undistinguishable why the impaired mitochondria are not completely cleared in sporadic Parkinson's disease. Current treatment primarily focuses on ameliorating the motor symptoms of Parkinson's disease targeting the dopaminergic system. Therefore, it is necessary to explore the underlying cellular and molecular

mechanisms that could help in determining therapeutic treatments of the disease wholly and not just symptomatically. Owing to the infamous presence of factors such as genetic defects even in sporadic PD, mitochondrial dysfunction should definitely be addressed more significantly in sporadic Parkinson's disease.

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