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The Factors Associated with Parkinson's Disease and the Current Treatment on PD

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Abstract. Parkinson's disease (PD) is neurodegenerative disease that occur in 1% of people in their sixth and subsequent decades. The classical of PD symptoms include of tremors, bradykinesia, muscle stiffness, and loss of balance, and are associated by the reduced function of degenerative neurons and intracellular accumulation of abnormal proteins. The exact causation of PD is unknown, with environmental and genetic factors showing relation to PD. Genetic mutations and environmental toxicants, such as pesticides, are related with an elevated incidence of PD, according to epidemiologic research. Several investigations carried in animal models confirmed this association. Currently no treatment can retard or halt the disease progression, including the most commonly used therapy which is the replenishment of striatal dopamine through oral administration. This do alleviate most of the symptoms, but it also introduces several side effects including dyskinesias. At present, gene therapy is not used in the treatment of PD; rather, it is only employed in disease trials. The non-disease modifying treatments have been showing encouraging results while the disease modifying treatments hold a greater potential.

Keywords: Parkinson's Disease, Environmental Factors, Genetic Factors, Treatment.

1. Introduction

In 1817 James Parkinson first introduced and defined a neurological disorder in a book that William Rutherford Sanders later called Parkinson's disease (PD) [1]. It is a neurological disease that has symptomatic characterization of uncontrollable tremors, bradykinesia and stiffness of body parts, and imbalance in coordination. At present, PD cannot be cured, and the treatments provide very limited and temporary relief from symptoms. At any given time and in any unselected group, PD incidence ranges from 5/100000 to 35/100000. PD affects 1% of the population in the sixth decade of life, increasing to 4% for the elderly aged 90 or above. Men are more susceptible to this disease than women, and people of all ethnic can be affected. The onset age is usually in the 60s; however, in the case of young-onset PD, which takes up 5-10% of all cases, the onset can be as early as between 21–40. From 1990 to 2016, the incidence of PD grew from 2.5 million to 6.1 million people [2]. This increased prevalence is due to improved methods in detecting and diagnosing PD, longer life expectancy and population aging, and increased exposure to environmental toxins, possibly due to industrialization.

The etiology of PD in the majority of documented instances is unclear, but a known range of environmental and genetic risk factors act as risk factors. The core cause of PD is the dopaminergic

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neurons of SNpc, which died in large numbers. This consequently results in striatal dopamine shortage within the basal ganglia, which causes the major symptoms. The accumulation of α-synuclein containing lewd bodies is found in the remaining neurons. [3] After having a general idea of the background and mechanism of PD, this paper will inform you about the pathology of PD and review currently existing risk factors associated with PD, this includes family history, environmental toxins, and advancing age. Then this paper will focus on the available treatments for PD, evaluate their effectiveness, and include the potential use of gene therapy on PD.

2. Pathology of PD

The death of those cells linked with PD, with the ventrolateral tier most impacted, including neurons projected to striatum. This region has moderate to severe cell losses, and it is high likely to be the origin of motor characteristics of PD, in particular, stiffness of body parts and bradykinesia. In PD, the loss also occurs in other region.

Lewy bodies are especially observed in certain medium to large-sized monoaminergic and cholinergic neurons in PD. The most sufficient protein in the related protein inclusion is α-synuclein, and the discovery of its gene SNCA, which mutation of this gene causes a monogenic form the PD [4]. When the protein is misfolded, α-insoluble synuclein create inclusions in cell and neuronal processes. Lewy pathology can also be found in the vagus nerve, sympathetic ganglia, CNS and PNS, saliva glands, adrenal medulla, and sciatic nerve [5].

Braak and his colleagues' study of Lewy bodies led to the discovery and classification of PD's effects on the central nervous system into six phases. (Table 1) Their study explains the clinical course of PD. Phase 1 and 2 have symptoms that can fit into the onset of premotor symptoms, phase 3 could correlate to the motor symptoms because the loss of nigrostriatal dopamine, and phase 4 to 6 corresponds to the non-motor characteristics. The linkage between Lewy pathology and non-motor symptoms shows significant signs of cognitive impairment in PD. In patients, the presence of other non-motor symptoms is associated with the Braak staging system, with no clear results to date [4]. The model proposes that Lewy pathology in PD progresses temporally and spatially [7].

Human post-mortem brain histology indicates evidence of mitochondrial malfunction, notably oxidative stress, a frequent pathogenic mechanism involved in the pathology of PD. In fact, MPTP exposure have very close features to PD due to mitochondrial inhibition and introduces dysfunctional mitochondria in PD symptoms. The decrease of mitochondrial complex 1 activity has been successfully linked to the degradation of dopaminergic neurons [4-6], which are susceptible to mitochondrial ROS. It is formed predominantly at complex 1 by the electron leak via the partial reduction of molecular oxygen to superoxide radical. ROS accumulation causes extensive damage to biological components. Dopamine is oxidized to create quinones and free radicals with in brains of Parkinson's patients. Other oxidation products of dopamine include aminochromes and superoxide radicals. Furthermore, mutations in mitochondrial dynamics are being studied. Mitochondria undergo fusion/fission dynamics to identify damaged populations for mitophagy in order to maintain a healthy population. Mitophagy activates the Parkin/PINK1 pathway, and the loss of PINK1/Parkin-based mitochondrial quality control due to genetic mutation contributes to the pathophysiology of PD [4,7].

3. Genetic Factors

There is no apparent family linkage in most people with PD, and approximately 15% of the patients have close relatives who have PD. Although they typically show no transparent mode of inheritance, the discovery of five genes and four other gene loci in familial PD invoked much more research into genetics. So far, mutations in nine genes have been found to cause most familial PD manifestation; these genes are α-synuclein gene (SNCA/Park1), LRRK2, PINK1, DJ-1, ATP13A2, UCHL1, VPS35, GBA1, and Parkin [6].

SNCA is the first gene correlated to autosomal dominant PD. Mutations in SNCA include missense mutations that may result in amino acid replacement, and increased protein production due to gene locus duplications makes α-synuclein susceptible to aggregate formation. SNCA-related PD is an

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uncommon gene mutation, however the identification of it as a genetic determinant of PD led to the recognisition of α- synuclein. LRRK2 mutations are strongly associated with familial PD with late-onset. Mutated LRRK are the most frequent genetic factor associated with PD, and they create synaptic dysfunctions by phosphorylating auxilin protein. Worldwide, LRRK2 mutations contribute to about 4% of familial PD and 1% of sporadic PD. DJ-1 is a deglycase protein that suppresses the aggregation of α-synuclein [4]. In the absence of DJ-1, α-synuclein aggregates more readily (in animal models). The location of DJ-1 inside the mitochondrial matrix is related to the pathophysiology of Parkinson's disease. ATP13A2 specifically encodes for a P5-type ATPase 13 A2 protein. Mutation in APT13A2 shows relations to dysfunctions of cell by reducing oxygen consumption and mitochondrial membrane potential [8]. The inheritance of its mutations leads to the development of PD in adolescents. Parkin and Pink1 genes are critical for the quality regulation of mitochondria. This requires the specific need for PINk1 to damage mitochondria and subsequently activates Parkin's E3 ligase to initiate autophagy [9]. The process of selective autophagy is impaired by PINK1 or Parkin mutations. The deubiquitinating enzyme encoded by the UCHL1 gene is essential for axonal integrity. The co-localization of UCHL1 and α-synuclein in LB of PD nigrostriatal neurons is found in immunohistological studies, and post-translational modifications in UCHL1 show relation to neurodegeneration underlying PD [8]. GBA1 (glucocerebrosidase 1) codes for a lysosomal enzyme, and its mutation increases the risk of developing PD earlier. GBA1 mutation D409H decreases the average lifespan and increases morbidity in mice transgenic with A53T -synuclein. These gene mutations are strongly correlated with PD (PD) pathology and are associated to malfunctioning mitochondria and their dynamics, lysosomal functions, and defective autophagy [4].

4. Environmental Factors

4.1. Pesticides

MPTP formed during the synthesis of a meperidine analog is found to cause permanent symptoms of PD by destroying dopaminergic neurons in substantiating nigra. MPTP is related to a certain extent to pesticides in the causation of PD. Pesticides are one of the most extensively studied PD risk factors over the last few decades. A meta-analysis of 46 studies revealed the risk ratio of 1.6 for exposure to pesticides on a regular basis vs never. A few indicators of variability in the research outcomes. Environment and Health Perspectives 120:340–47) The ratio was greatest for insecticides and herbicides, as well as investigations that did not depend on self-reported exposures, since the majority of farmers are unaware of the chemical to which they were exposed. Pesticides have been the subject of several research, which are summarized in Table 1 [10].

Table 1. Pesticide uses and PD [11].

Investigation	Design	Exposure	Risk ratio, 95% CI
Hertzman et al.	Retrospective studies	Spraying of pesticides	6.6, p = 0.031
		Paraquat	nc, p = 0.01
Semchuk et al.	Retrospective studies	Application of pesticides	2.3 (1.3–4.0)
		Herbicide use	3.0 (1.2–7.3)
Liou et al.	Retrospective studies	Pesticide exposures	2.9 (2.3–3.7)
		Paraquat	3.2 (2.4–4.3)
Petrovitch et al.	Cohort study	Plantation work	1.9 (1.0–3.5)
Baldi et al.	Cohort study	Occupational pesticide exposure	5.6 (1.5–22)
Baldereschi et al.	Nested case-control study	Pesticide-use license	3.7 (1.6–8.6)
Ascherio et al.	Cohort	Any pesticide exposure	1.8 (1.3–2.5)
Kamel et al.	Nested case-control study	Professional pesticide use	2.3 (1.2–4.5)
		Paraquat	1.8 (1.0–3.4)
		DDT	1.0 (0.6–1.8)
		2,4-D	0.9 (0.5–1.8)

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Table 1. (continued)

Dick et al.	Retrospective studies	Pesticide use	1.3 (1.0–1.6)
Hancock et al.	Familial study	Pesticide application	1.6 (1.1–2.3)
		Organochlorines	2.0 (1.1–3.6)
Firestone et al.	Retrospective studies	Pesticide worker	1.5 (0.5–4.4)
		DDT	0.8 (0.4–1.6)
		2,4-D	0.8 (0.3–2.0)
Gatto et al.	Retrospective studies	Well water inferred exposure	
		Diazinon	1.6 (1.0–2.4)
		Chlorpyrifos	1.5 (0.9–2.2)
		Propargite	1.3 (0.9–2.0)
Tanner et al.	Retrospective studies	Occupational pesticide use	1.9 (1.1–3.2)
		Paraquat	2.8 (0.8–9.7)
		Permethrin	3.1 (0.7–15.8)
		2,4-D	2.6 (1.03–6.5)
Elbaz et al.	Retrospective studies	Pesticide application	1.8 (1.1–3.1)
		Organochlorines	2.4 (1.2–5.0)
Tanner et al.	Retrospective studies	Rotenone	2.5 (1.3–4.7)
		Paraquat	2.5 (1.4–4.7)
		Dieldrin	1.6 (0.7–3.3)
Wang et al. 2011	Retrospective studies	Ziram + maneb + paraquat	
		Occupational exposure	3.1 (1.7–5.6)
		Residential exposure	1.9 (1.1–3.2)
Fitzmaurice et al. 2013 (205)	Retrospective studies	Benomyl (highest quartile)	
		Occupational exposure	2.0 (1.3–3.0)
		Residential exposure	1.2 (0.8–1.9)

4.2. Rotenone

Rotenone is an insecticidal poison widely used in agriculture for the inhibition of the electron transport chain in complex I, the exact site that PD affects, causing neurotoxicant MPP. In animal models, rotenone reduces ATP production by impairing mitochondrial function, generating ROS, activating microglia, and impairing proteasome function. In addition, it induces selective degradation of dopaminergic neurons, buildup of protein aggregates, and a PD's syndrome characterized by bradykinesia, stiffness, tremor, and non-motor symptoms [10,11].

4.3. Paraquat

Paraquat is a herbicide that has a similar chemical structure with MPP+. Dopamine transporter was absorbed after being converted to paraquat+, similar to MPTP. By generating superoxide radicals and engaging in redox cycling, paraquat creates substantial levels of reactive oxygen species (ROS). In animal experiments, it generates a parkinsonian condition that replicates several PD symptoms. It causes peroxidation of lipid, decline levels of antioxidants, leads dysfunction mitochondria, and others. It is probable that the enhanced sensitivity of nigral dopaminergic neurons to oxidative stress contributes in part to its higher selectivity for these neurons. At least, some studies have linked it's exposure to an increased risk of PD, while others show no relationship. Particularly, the risk increased by more than double among pesticide applicators who used paraquat [11]."

4.4. Oranochlorines

Organochlorine pesticides show most frequent relation to PD. Dieldrin is a organochlorine pesticide that was widely used between 1950 and 1970 and for termite control between 1972 and 1987. In culture, it is toxic to dopaminergic neurons and depletes dopamine in the brains of several animal species. Dieldrine mimics many pathogenic pathways of Parkinson's disease. It increases microglia,

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inhibits personal mitochondrial oxidative phosphorylation, and reduces ATP levels. Dieldrin enhances the fibrillization and aggregation of -synuclein protein of the mouse mesencephalon and inhibits its degradation through the ubiquitin-proteasome pathway. Researchers found the higher levels of it in blood samples before to the onset of PD, whereas others fount it in brain specimens. All of them suggest a link between dieldrin and PD [11].

4.5. HCHs

Hexachlorohexanes (HCHs) have eight isomers, one of which is γ-HCH (lindane), and this was used as an insecticide beginning at last century. Its agricultural use of it was banned worldwide in 2009. This works in humans for treating scabies and lice. In the animal model, one dose causes noticeable losses in the number of brain dopamine. In rodents, lindane increases microglial reactive oxygen species (ROS). In humans, the level of γ-HCH is four times greater in PD patients than in no-affected region.

β -HCH, the second isomer form of Hexacholorohexanes, has likewise been consistently linked to PD. About 76% of PD patients had it in their serum, which is far greater compared to about 39% in non-PD individuals. In a larger research, those with a high levels of HCH was tripled increased risk of developing Parkinson's disease [10-12].”

4.6. 2,4-Dichlorophenoxyacetic acid (2,4-D)

2,4-D is currently available as the one of the element in Agent Orange. The institution of medicine includes this as a potential risk factor. Although there is a strong association between 2,4-D exposure with increased risk in a study, no correlation was found in other studies. In the animal model (mice), no noticeable changes were found in the dopaminergic function after exposure to acute 2,4-D [11,12].

4.7. Dithiocarbamates

A widespread kind of fungicide, dithiocarbamates include maneb, zineb, ziram, and various analogs. Maneb induces selective dopaminergic neurotoxicity in mice by disruption of mitochondrial activity, elevation of oxidative stress, and inhibition of proteasomal function. By blocking the E1 ligase of the ubiquitin-proteasome system, Ziram causes harm to dopaminergic neurons. pidemiological studies that computed it exposures revealed that maneb, ziram, and zineb were linked with an increased risk [11,12].

4.8. Orangnophosphates

This type of pesticides include malathion, diazinon, and many more. Inhibition of acetylcholinesterase leads to hyperactivity of cholinergic neurotransmission, which has an insecticidal effect. Chlorpyrifos tends to decrease immunoreactivity and change dopamine signaling. In culture, it reduces mitochondrial Complex I function, modifies the shape and motility of neuronal mitochondria, and raises oxidative stress indicators. PD risk was connected with inferred exposure to those drugs, and two investigations revealed that occupational usage of methyl parathion enhanced the risk [11,12].

4.9. Pyrethroids

Permethrin in the pyrethroids pesticide family disrupts the voltage-gated sodium channels and at high concentrations, it inhibits mitochondrial Complex I and lowers mitochondrial integrity while increasing striatal dopamine turnover. A tendency toward higher PD risk linked to permethrin usage has been seen in at least two epidemiologic investigations, although statistical power was inadequate [11,12].

4.10. Pesticide Summary

Most individuals exposed to pesticides do not develope PD. but the studies show the link between it and PD, supported. These data are further supported by experiments in an animal model which mimics and illustrates PD pathology [10-12].

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5. Lifestyle Risk Factors

Interestingly, many studies have found that smoking decreases the risk of developing PD. The risk of frequent smokers developing PD is halved compared to never-smokers. Surprisingly, PD patients can quit smoking more quickly, possibly because of the decrease in the responsiveness to nicotine. Caffeine and coffee also decrease the risk of developing PD to a similar extent to smoking [13].

6. Treatments of PD

6.1. Medical treatments

Medical treatments for PD include pharmacotherapy and non-pharmacotherapy to treat the symptoms of PD. Pharmacological therapy for PD mainly involves dopamine. Levodopa preparation, monoamine oxidase, and dopamine agonist are helpful in initial therapies. Anticholinergic medications are beneficial for juvenile-onset PD patients with pronounced tremors, while their adverse effects must be closely controlled. In comparison to those initially treated with MAO-B inhibitors and/or dopamine agonists, random distribution of levodopa to PD patients has small but long-lasting mobility advantages after a few years (normally seven), as measured by the average score on the PD Questionnaire-39 mobility subscale (10 items ranging from 0 to 40). Although the difference between each test bodies were not notable, levodopa-treated patients had a greater likability to cause dyskinesias. The probability of canceling the study on medicinal effects to participants in dopamine agonists (50%) and MAO-B inhibitors (72%) was also greater than participants who received levodopa (7%), generally due to side effects [8,12].

More than forty percent of patients treated with oral dopamine agonists develop impulse control issues, and between fifteen and twenty percent of those who quit dopamine agonist usage owing to unfavorable effects experience withdrawal symptoms. Therefore, dopamine agonists cannot often be terminated despite their significant side effects [8].

The selection of the starting treatment of PD requires careful comparison and weighing of the risks and benefits due to different degrees of cure and side effects. Using of levodopa leads to improvements in functionality but as enhances the probability of acquiring dyskinesia as a side effect, especially those with high doses. Dopamine agonist and MAO-B inhibitors are less effective in terms of easing the symptoms but are less likely to develop dyskinesia. Consequently, the majority of PD patients use a mix of drugs to provide complementing advantages while minimizing excessive dosages associated with bad effects. Overtime, due to drug tolerance or loss of levodopa's efficacy, PD patients often need more frequent levodopa administration. As PD progresses, due to disease-related pathophysiological changes in the brain, patients will have a shorter duration of dopaminergic drug response [8].

There is various medication work associated with levodopa to enhance the effectiveness of therapy. Dopamine agonists and MAO-B inhibitors are dosed daily with a usual frequency of 3 times per day, which is less frequent than the required doses of levodopa. Inhibitors of catechol-O-methyltransferase and monoamine oxidase B extend the therapeutic effects of levodopa. Quicker medication response can be achieved using inhaled levodopa (administrated orally via an inhaler) and subcutaneous apomorphine injections (self-administrated with an injection pen) to treat patients with off periods and delayed onset PD. Each of these treatments may be administered up to five times per day. It is possible to treat dyskinesias by lowering dopaminergic medicines or by adding amantadine. The immediate release of amantadine is not approved by the FDA, while the FDA approves 2 extended-release preparations [8].

Non-pharmacotherapeutic therapies, such as gait and balance training, are examples of non-pharmacotherapy. Strength training, cardiovascular exercise, dance-based programs, and tai chi. Each training modality helps distinct motor components of PD. Occupational therapy, physiotherapy, and language therapy are also beneficial. Interventions in physical therapy may assist preserve or enhance motor symptoms, balance, and function, as well as providing solutions for managing hypophonia and

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dysphagia. Referrals to multidisciplinary therapy consultations are crucial to the provision of effective PD care [8,14].

6.2. Gene therapy

AADC is an enzyme belong to the synthetic dopamine apparatus and is in charge of converting L-DOPA to dopamine. L-DOPA, a symptomatic medication that cannot prevent disease development and has adverse effects, is the first treatment for PD. OFF-states are times of motionlessness and inability and are usually accompanied by melancholy or hypomania. This is related to erratic stomach emptying, an excess of the BBB carrier system, which responsible for delivering L-DOPA, and inadequate amounts of aromatic L-amino acid decarboxylase. Using different L-DOPA formulations and pump technologies, the absorption problem has been resolved. Several mouse investigations shown that stratal AADC overexpression related to vectors was well tolerated and ameliorated PD symptoms [16].

According to subsequent studies conducted on non-human primates, there was a decrease in the need for medication at a specific level of transfection. In 2008, in the publication of a phase 1 clinical experiment data involving the use of bilateral AAV2-induced AADC expression in the putamen of severely afflicted the patients. The researchers discovered a descent increase in the PD rating scale and there were no adverse effects found in humans after the treatment. More importantly, this clinical trial showed better symptomatology, and overall reduced PD rating scale and decreased requirement for L-DOPA. AADC ligand Fluoro-L-m-tyrosine activity decreased and somewhat in a follow-up analysis of patients from a phase 1 research. The scientists ascribe the drop to the continuous degradation of non-transfected, still-functioning nigral neurons, suggesting that AAV treatment is permanent and the expression of transfected cells does not diminish with time. Currently, two studies are being conducted to explore and ensure the safe use of AADC treatment by optimizing dose and administration [16].

All the participants in the clinical trial show encouraging results in reduced use of levodopa and in the PD rating score. This offers a great potential for future use of AADC gene therapy on PD patients.

6.3.1. Disease Modifying Targets. The focus of this paper is on GDNF and NRTN. Other factors that are not included in this paper, but are helpful in gene therapy as well, this includes artemin (ARTN) and perception (PSPN) [16].

6.3.2. GDNF and NRTN. GDNF direct administration shown that it can stimulates neurite sprouting and showed a decreased PD manifestation in PD toxin models. This phenomenon was seen in phase 1 trials only. Insufficient impact of GDNF infusion is linked to the limited distribution of the medication, which may have been caused by a pump failure and a lack of remaining neurons for GDNF to influence. Consequently, the therapeutic gene strategy was investigated. In some animal models, AAV-GDNF injected into the putamen is shown to be a secure and effective treatment for PD manifestation in murine models. By administering tetracycline, this approach permits the regulation of GDNF expression, making otherwise constant expression manageable owing to the need for external stimulation. Yurek et al. (2017) revealed a novel method for delivering GDNF gene therapy to the midbrain of rats using nanoparticles composed of a lysine polymer and GDNF with plasmid inside. The demonstration of treatment with 6-OHDA enhanced rotational behavior in the cylinder test and resulted in a greater number of outstanding TH+ cells. In aged and MPTP-treated monkeys, the anti-parkinsonism efficacy of overexpressed GDNF in dopaminergic neurons was examined and found to be promising. The American phase 1 trial is approved by the FAD to examine the effect in the delivering of AAV2-GDNF vector to the putamen over a year [16].

NRTN is dependent on the co-receptor GFR2 and has been demonstrated to enhance motor function in both mice and non-human primates. In animal models NRTN trial haven been showing encouraging results, and later phase 2 study using the same methodology failed to fulfill its main goal, since no statistically notable change in motor scores between the test group and the controlled group at the follow-up study. At the 18-month follow-up, a substantial increase in self examined and reported

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activities of daily living, along with a modeset improvement in motor scores. These indicate the impact of AAV2-NRTN is being delayed. Bartus's examinations of six participants from clinical study investigating the delivery of AAV2-NRTN to the putamen suggested that longer exposure to it was related with increase of TH-positive cells. The failure the research to accomplish its main aim may have been attributable to a low transfection rate or a probable lack of retrograde transport in nigral dopamine neurons after delivery of the vector through the putamen. In a subsequent clinical experiment, it was shown that the administration into the SN, the putamen and greater vector titers, lowered the UPDRS scores in the participants. Unfortunately, the second randomized phase 2 study using the same methodology, with a follow up study of a length of15 to 24 months, was similarly unsuccessful in achieving the main goal, since AAV2-NRTN was not shown to be better than sham surgery in increasing motor scores. The apparent therapeutic advantage of GDNF and NRTN in non-masked trials may attributable to placebo effects, which may explain why the successful findings from phase 1 research failed to be confirmed in phase 2 studies. The evident impact of CFLs in the 6-OHDA and MPTP models are not likely to be applicable in the evaluation of growth factors, since the animal models show no representation in PD pathology. After injection into the striatum, a significant number of the animal experiments listed in this publication depend on the retrograde transit of gene therapy vectors produced in the SN. However, some studies show that SNCA inhibits intracellular transport through impairing the Golgi apparatus. Post-mortem research on humans have shown the same transport problem. This suggests that it may be prudent to explore several injection sites when evaluating antiparkinsonian vectors. In animal models studying the impact of GDNF on PD behavior, no positive was found. Therefore, decreased hypothesized that the failure of this trials might be attributed to the presence of SNCA, which inhibits the production of Nurr1 and disrupts the pathway allowing the neuroprotective activity of GFL. This seems to contradict the reported neuroprotective effect of GFL expression alone. Nevertheless, caution may be advised given that the SNCA model employed in these works seem to express SNCA at a much higher level than PD and other alpha-synucleinopathies [16].

7. Conclusion

PD is a multifactorial neurological disease which involves a number of impaired mechanism pathways and., consequently a complicated clinical manifestation and treatment. Dysfunctional mitochondria, oxidative stress, neurodegeneration and aggregation of alpha-synuclein are classic causes. Genetic and environmental factors that disrupt these processes are expected to be risk factors for PD. Investigation and understanding of genetics' effect on the molecular and cellular processes implicated in neurodegeneration are critical in the research direction. These studies offered the use of medication that can ease PD symptoms but introduce adverse effects. The use of Gene therapy in the theoretical trials targeting non-disease and disease-modifying targets with encouraging results makes this a viable prospective therapy for PD. The experimental and clinical outcomes of non-disease-modifying therapies are promising. The efficacy of disease-modifying treatments in halting or reversing the course of PD is not yet known. From the discovery of several PD-related genes and disease-causing pesticide components, a number of long-term objectives are apparent. Future research should investigate the relationship between the molecular and cellular pathways altered by disease-related variables. Although gene therapy has not yet provided a definitive cure for PD, there is growing evidence to suggest that it will become a key component of future PD treatments.

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