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POTENTIAL TARGET THERAPY AND DRUG TREATMENT FOR PARKINSON'S DISEASE

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ABSTRACT

Parkinson disease (PD) is a neurodegenerative condition that worsens over time and is mostly caused by the death of dopaminergic neurons in the substantia nigra. This loss results in bradykinesia, rigidity, and tremors, among other motor symptoms. Disease-modifying medicines are still needed, despite advances in treating symptoms. Beyond dopamine substitution, novel research is increasingly concentrating on possible treatment targets. Over 6 million people globally suffer with Parkinson's disease. PD is characterized by motor impairments that are linked to the gradual death and degradation of dopaminergic neurons in the pars compacta the majority of patients can only access or benefit from the most widely used PD treatments, which are either partially or momentarily effective. More potent treatments are desperately needed because current ones neither stop the disease's progression nor replace lost or degraded dopaminergic neurons. We offer a thorough review of the state of knowledge on the molecular signaling pathways connected to Parkinson's disease (PD), with a focus on how environmental and genetic factors influence the development and course of the disease. Additionally emphasized are the roles played by proteasome systems, autophagy-lysosomal pathways, and molecular chaperones in Parkinson's disease. Furthermore, new treatment approaches to stop or slow the advancement of this complicated illness are examined, including gene therapy, stem cell transplantation, pharmaceutical interventions, and complementary, supportive, and rehabilitation therapies.

KEYWORDS: Cell treatment, Parkinson's disease, misfolded proteins, neurodegeneration, Cell therapy.

INTRODUCTION

Parkinson's disease is characterized as a chronic, progressive neurodegenerative disorder that mainly affects the motor functions of the central nervous system (CNS) as a result of dopamine depletion in the substantia nigra, pars compacta (SNpc), and loss of dopamine-producing neurons in this important region of the brain that regulates movement. Tremor, bradykinesia (slowness of movement), rigidity, and postural instability are some of the disease's prominent symptoms. One of the main theories for Parkinson's disease (PD) is the misfolding of proteins and their subsequent accumulation in intracellular compartments.[1] There is experimental data that suggests Parkinson's disease (PD) also affects the frontostriatal pathways, anterior cingulate gyrus, and/or prefrontal cortex (PFC).[2] Despite this, it is unclear exactly how dopaminergic neuronal loss occurs in SNpc. The development and course of Parkinson's disease (PD) may be influenced by a number of factors, including mitochondrial damage, energy deficiency, oxidative stress, excitotoxicity, protein misfolding and aggregation, disruption of protein clearance pathways, cell-autonomous processes, and "prion-like protein infection." Among these, the buildup of misfolded proteins in intracellular spaces has emerged as a prominent theory for Parkinson's disease (PD). Lewy bodies (LB), which include many misfolded amyloid proteins, including phosphorylated tau (p-tau), amyloid beta protein (Aβ), and alpha-synuclein (SNCA), are the main misfolded amyloid protein inclusion seen in the intracellular spaces of SNpc neurons in Parkinson's disease (PD). Numerous environmental pollutants are linked to sporadic Parkinson's disease (SPD), which can be partially replicated in PD experimental animal models.[3] Two such toxins are paraquat and 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP). It is more challenging to comprehend the pathophysiology of PD because familial cases, in contrast to SPD, are uncommon and do not exhibit the typical signs of PD. Despite the development of numerous new PD medications, none of them have been able to stop the disease's progression. Only a small percentage of patients can benefit from the few symptomatic therapies that are now available. Furthermore, the main obstacles to using these medications to treat Parkinson's disease are their permeability, short half-lives, and adverse effects. Curiously, new advances in gene treatments and stem cell transplantation have garnered particular interest as alternate approaches to addressing PD. For instance, in mice models of Parkinson's disease, genetically altered DA neurons have demonstrated encouraging outcomes. Similarly, scientists are able to fix some of the defective metabolic pathways linked with Parkinson's disease (PD) by employing lentiviral or recombinant adenoassociated viral vectors (rAAV). Moreover, CRISPR-Cas9, a relatively recent advancement in the gene editing method, may help treat

Parkinson's disease. It stands for clustered regularly-interspaced short palindromic repeats associated protein 9.[4] The goal of this study is to present fundamental conceptual knowledge on the molecular mechanisms behind Parkinson's disease (PD), in light of the urgent need for the development of novel, sensible therapeutics. This knowledge may be useful in the creation of more potent medications or alternative treatment approaches. Industrialized nations as a result of a rise in the elderly population. The main risk factor for Parkinson's disease (PD) is aging. As a result, PD instances are extremely rare in those under 40 and increase in frequency as one gets older. In people who are 70 and 80 years old. Individuals who have PD sufferers who are one or more close relatives have an in increased likelihood of contracting the illness directly, although the entire danger is still only 2-4 percent, barring a family with a known mutation in the disease's gene. Other there are risk factors, such as environmental exposure poisons. But the majority of scientists concur that PD is not a deadly illness in and of itself; rather, it causes normal functioning to gradually deteriorate. It's interesting to note that the typical lifespan of a PD patient is typically the same as for average individuals.[5]

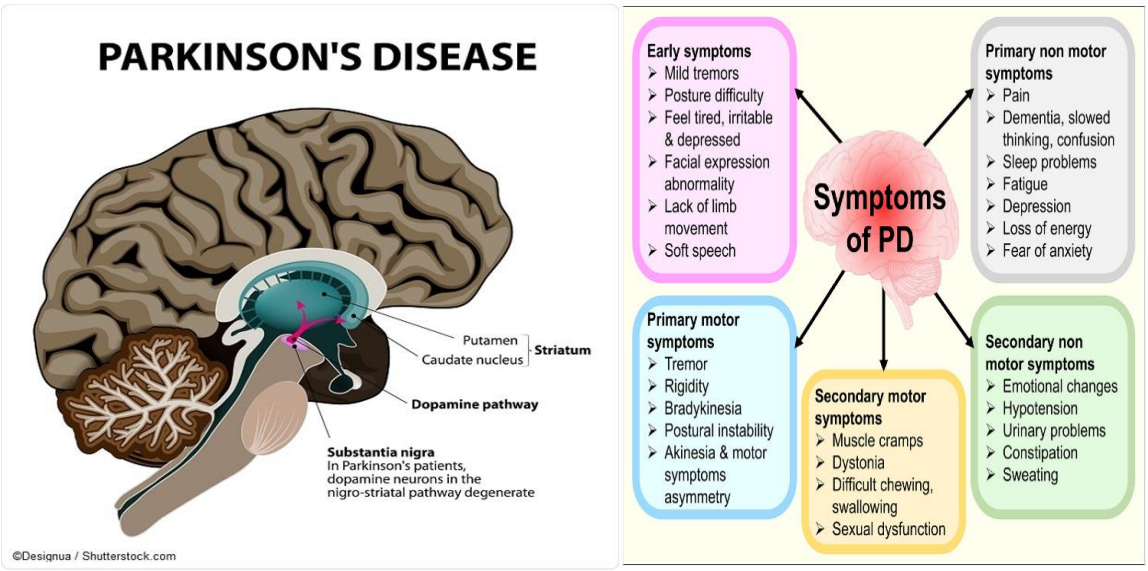

Figure Number 1: internal structure of brain and different symptoms of Parkinson's disease.

EPIDEMIOLOGY OF PARKINSON'S DISEASE

Although methodological variations make it difficult to compare the incidence of Parkinson's disease across research, certain conclusions can be drawn. After Alzheimer's disease, Parkinson's disease is the second most prevalent neurological illness. In high-income nations, the disease has a median age-standardized yearly incidence rate of 14 per 100000 persons

overall and 160 per 100000 those 65 years of age or older. Lifespan risk is a potentially more comprehensible indicator of the frequency of a disease. It was estimated to be 2% for men and 1.33% for women in the USA for those over 40, accounting for competing hazards like mortality from cancer or cardiovascular disease.[6] Africa appears to have a lower age-adjusted Parkinson's disease prevalence, which accounts for both incidence and mortality. As opposed to the Americas and Europe. Asia's incidence is comparable to that of Europe and the Americas. One study conducted in New York, USA, found that the disease was more common in black individuals than in white individuals. Another study found that among participants in a major US health organization, the age- and sex-adjusted incidence of Parkinson's disease was highest in Hispanic individuals (16·6 per 100 000 people), followed by non-Hispanic white people (13·6), persons (11·3) and African Americans (10.2) Based on a case study among US Medicare enrollees, prevalence was also greater in white individuals than in Asian or Black individuals. Black folks (10·2) and Asian people (11.3). In another study, the incidence was higher in white individuals than in black or Asian individuals, based on US Medicare beneficiaries. While the overall prevalence of Parkinsonism remained steady, there was a reported 6% annual drop in the incidence of Parkinson's disease in the UK between 1999 and 2009[7] This decline was attributed to improved diagnosis of other parkinsonian disorders. In contrast, it has been claimed that in Rotterdam, Netherlands, both Parkinson's disease and Parkinsonism decreased between the years 1990 and 2000-10 and that in Minnesota, USA, they increased between 1976 and 2005.

Parkinson's disease is uncommon before the age of 50, but as people age, their risk of developing it rises quickly, with most studies showing a peak around the age of 80. Most likely as a result of under diagnosis as people age. The rising prevalence of dementia, which is an exclusion criterion for the diagnosis of Parkinson's disease when present at the outset of motor symptoms, is likely to induce a misleading decline in the incidence of Parkinson's disease with aging. In most studies, the male to female incidence ratio falls between around 1·3 and 2·0. However, rates as low as 0·95 have been reported in Asia, which may be due to sex variations in smoking behaviour and will be covered in more detail later in this Review.[8]

RISK FACTORS

1) Dairy goods.

2) Chemical pesticides.

3) Methuselination-Related Cancer.

4) Traumatic brain damage.

5) Diabetes and the body mass index.

6) Hypertension and blood cholesterol alcohol.

7) Hormones after menopause and reproductive aspects.

8) Micronutrients, including vitamins.

9) Other macronutrients and fat.[9]

NEW CLINICAL SUBTYPES OF PARKINSON'S DISEASE

The clinical features and natural course of Parkinson disease (PD) vary widely, supporting the notion that PD may be a syndrome rather than a single disease. The National Institutes of Health recently ranked subtype identification among the top three clinical research priorities for progressing PD. This categorization is necessary to better understand the pathophysiology based disease mechanisms, prognosing of PD progression and non-causal interventions for novel personalized treatment strategies. It is more of a hypothesis free data driven approach that tries to divide patients into different categories based upon clinical features. Previous studies have used cluster analysis to define clinical PD subtypes based on motor severity, presence of abnormal movements (motor complications), some non -motor features and age at onset. The depth of phenotypic information was variable… most studies were cross-sectional in nature, and with few exceptions used little or no longitudinal assessment to assess prognosis within subtypes In 2005 we began the collection of comprehensive data on a PD cohort that included standardized motor testing, an extensive profile of nonmotor manifestations, neuropsychological evaluation, polysomnography[10] This allows the possibility to cluster deep phenotyping followed by validation of the subtypes in prospective studies. Based on this background, the aimed to be studied.

(1) Identify clinical subtypes of PD with cluster analysis,

(2) Investigate the rate of progression in these different clusters.

(3) Validate our clustering solution by comparing it against previously published similar solutions within the same cohort.[11]

METHODS

Enlistment of Participants

From 2005 to 2013, participants were recruited from the McGill University Health Centre and the Centre Hospitalier d'l'Université de Montréal's movement disorders clinics in Montreal, Canada. Patients who met the UK Brain Bank Criteria for Parkinsonism and whose

most likely etiology was determined to be idiopathic Parkinson's disease were eligible for enrolment. The following criteria were used to exclude patients: baseline dementia as defined by the Movement Disorder Society; diagnosis of other causes of Parkinsonism on baseline or follow-up examinations; and other criteria. The Montreal General Hospital's and Hospital du sSacre-Coeur de Montréal's ethical committees accepted the study protocol. All participants provided written informed consent, and the results are displayed in an anonymous manner.[12]

Initial Evaluations

When the patient was "on" medicine, assessments were conducted. The patient self-reported the duration of the disease as the period since the onset of the first symptom or indication of a cardinal motor Parkinsonism feature. These variables' complete description has already been released. Variables comprised the subsequent items.

Motor Types and Severity

• Subscales I through IV.10 of the Unified Parkinson's Disease Rating Scale (UPDRS);

• Hoehn and Yahr staging.

• Score for motor impairment "A" represents the total of the UPDRS-Part III items related to bradykinesia, tremor, stiffness, and facial expression (dopamine responsive); "B" represents the total of the UPDRS-Part III items related to speech and axial dysfunction (dopamine nonresponsive).

Difficulties with the motor

• Dyskinesia: UPDRS Part IV: 32–34 added together.

• Fluctuation: UPDRS Part IV: 36–39 added together.

Subtypes of Motors

• Gait-difficulty-postural instability score.

• The swallowing-freezing-speech score.

• Predominance of every fundamental sign of Parkinsonism.

• The onset's side.

• Ratio of axial to limb.

• Drooling, freezing, choking, and falls are present.

Motor Testing in Quantitative Form

• Up-and-go timing.

• The other Tap test.

Cognitive Status

• Mini-Mental State Examination.

• Evaluation of neuropsychology to record moderate cognitive impairment (MCI) Using five cognitive areas, MCI was initially described in accordance with the 2012 Movement Disorder Society Task Force standards. Additionally, this was categorized based on.

•Single domain versus multiple domain;

• subtypes

a) Impaired attention, executive functioning, episodic verbal memory (free recall), or a combination of these three domains can be found in the frontal domain.

b) Impaired visuospatial abilities can be found in the posterior domain. Patients were categorized as frontal plus posterior, frontal solely, or posterior exclusively.

Manifestations of Autonomy

•orthostatic hypotension (OH): manual measurements of systolic and diastolic blood pressure taken while supine and after standing for one minute.[13]

Psychotic Signs and Symptoms

• Depression: II. on the Beck Depression Inventory

• Beck Anxiety Inventory for Anxiety.

• UPDRS Part I–3 on Apathy.

• Hallucinations/Illusions: the Parkinson Psychosis Questionnaire's hallucinations/illusions part.

• Impulse control disorders: detailed interview on excessive spending, hypersexuality, compulsive gambling, paranoia, and punding.[14]

Disorders of Sleep

• the tonic and phasic rapid eye movement (REM) muscle activity percentage density during the course of a nocturnal polysomnography (PSG).

• Sleep behavior disorder (RBD): assessed using overnight PSG, which is characterized using PSG criteria and the diagnostic criteria of the International Classification of Sleep Disorders

• Cardiac autonomic dysfunction: determined by analyzing the ECG from awake PSG, assessing the frequency domains (high, low, and very low frequency) and the time domains (mean RR interval and RR standard deviation), evaluated in a selection of patients per previously published guidelines.

• Insomnia: Insomnia Severity Index.

• Epworth Sleepiness Scale for somnolence during the day. Particular Perceptions.

• Olfaction: 80% of age/sex-adjusted norms indicate hyposmia on the 40-item University of Pennsylvania Smell Identification Test.

• Color vision: Farnworth-Munsell 100 Hue test (impaired color discrimination = error score of >125% age-adjusted norms).[15]

Global Composite Outcome and Total Disease Severity

In order to assess the overall severity and prognosis, we categorized the factors based on the most important manifestations, which we distilled into four main categories.

1. Motor symptoms: total of Part II and Part IV UPDRS scores.
2. Part III score of UPDRS for motor symptoms.
3. Cognition was scored as follows: mild-to-moderate dementia (score = 3), severe dementia (score = 4), single-domain MCI (score = 1), multiple-domain MCI (scoring = 2), and normal.
4. Equal weighting of standardized (0–4) values for apathy, depression, anxiety, hallucinations, sleeplessness, insomnia, orthostatic dysfunction, urine dysfunction, and constipation are among the other nonmotor signs.

The standardized scores for these four categories were combined to form a global composite outcome (GCO). The quintile values of the several domains were added up to determine the final score (which ranged from 0 to 16). With the exception of cognition, which employed the same 5-grade status, the same cut-off values for baseline quintiles were used to measure overall illness severity in the assessment of progression.[16]

MOLECULAR MECHANISMS & PATHOGENSIS OF PD

Parkinson's disease (PD) is a complex illness that involves both hereditary and non-hereditary elements, like environmental factors. The accumulation of misfolded protein aggregates, malfunctioning protein clearance pathways, mitochondrial damage, oxidative stress, excitotoxicity, neuroinflammation, and genetic alterations are the most prominent factors implicated in the development of Parkinson's disease (PD).[17]

The part misfolded protein aggregation plays in Parkinson's disease (PD)

(i) Alpha-synuclein (SNCA) aggregation: The intracellular buildup of LB in DA neurons of the SNpc, which contain misfolded aggregates of SNCA and other related proteins, is one of the hallmark diseases of Parkinson's disease (PD). It's interesting to note that a number of molecular, genetic, and biochemical studies have demonstrated that the post-mortem brains of patients who were neuropathologically diagnosed as having mixed dementia with Lewy bodies (DLB) or Parkinson's disease with dementia (PDD) often exhibit a mixture of multiple misfolded protein aggregates, including p-tau, Aβ, and SNCA. Gomperts and colleagues looked at the brains of a number of people with Parkinson's disease (PD) and discovered a combination of amyloid deposition in their brains. This was connected to cognitive reductions without dementia, indicating that amyloid ages and contributes to cognitive but not motor decline. In a similar vein, Hepp and associates discovered that PDD and LBD cognitive deficits are influenced by the amount and load of Aβ pathology. A pore in the membrane can be created by the oligomers, proto-fibrils, and fibrils of SNCA or other misfolded amyloid proteins, which can lead to neuronal death through excitotoxicity, oxidative stress, energy failure, and neuroinflammation. A single intra cerebro ventricular (i.c.v.) for instance. Reduced TH and DA concentration in the caudate putamen, as well as late motor and non-motor symptoms such impairments in the pole and rotarod tests, are observed in mice infused with SNCA oligomers (α-SYOs). Comparably, familial Parkinson's disease (PD) is brought on by mutations in the SNCA gene (e.g., A53T, A30P, E46K, and H50Q), which has a strong correlation with dementia and an early onset. In animal and cell culture models, overexpression of SNCA resulted in a buildup of SNCA aggregates in the mitochondria, pronounced defects in mitochondrial mobility, and a reduction in the potential of the mitochondrial membrane. The electron transport chain was impaired in the SNCA deletion mice, and they displayed aberrant mitochondrial lipids. Additionally, the mice's susceptibility to mitochondrial toxins decreased. Additionally, a transgenic mouse model of Parkinson's disease (PD) called A53T has a substantial decrease in complex IV activity along with an accumulation of mitochondria carrying SNCA, leading to neural mitochondria degradation. There have also been reports of SNCA inclusion, respiratory chain failure, oxidative stress, and mitochondrial DNA damage in human DA-neurons in the PD brain.[18]

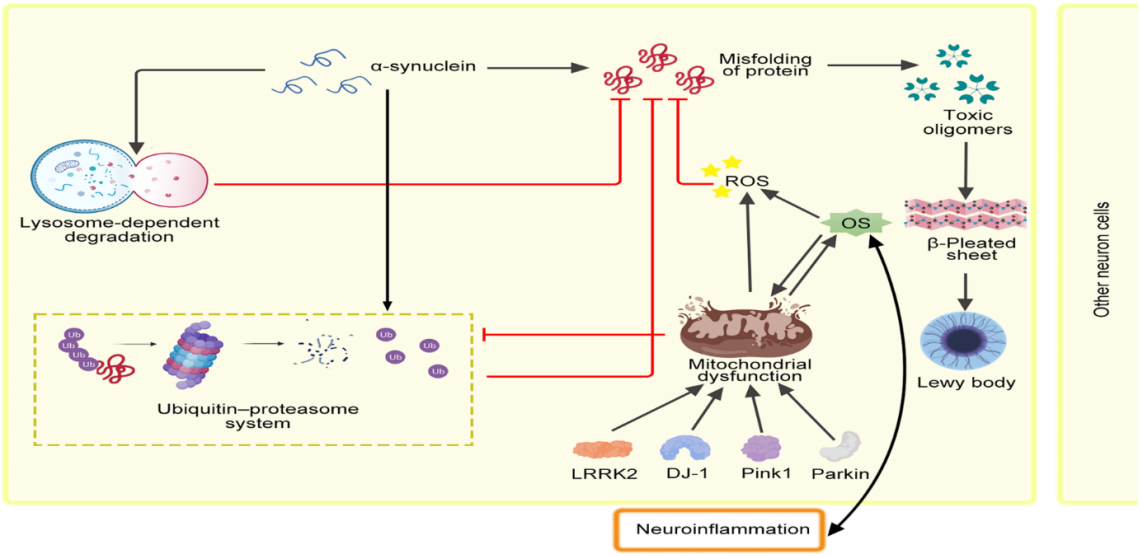

Figure Number 2: Intracellular α-synuclein homeostasis is sustained by the lysosomal autophagy and ubiquitin–proteasome pathways. α-synuclein buildup may be caused by impairment of these degradation processes by the operating system, mitochondrial malfunction, or neuroinflammation. Moreover, mutations causing mitochondrial malfunction and increased cell mortality are found in genes such as DJ-1, Parkin, Pink1, LRRK2, and DJ-1. Lastly, it seems that neuroinflammation and OS are related.

(ii) Tau. The accumulation of paired tau helical filaments, or neurofibrillary tangles (NFT), is a hallmark pathology of various neurodegenerative diseases, such as AD, frontotemporal dementia with Parkinsonism (FTDP), and progressive supra-nuclear palsy (PSP). Hyper-phosphorylation of tau (p-tau) can lead to this accumulation. Cortex and SNpc regions are the sites of p-tau accumulation in the FTDP, which is associated with chromosome (FTDP-17). It is also possible for the p-tau to colocalize with LB, which is frequently linked to the emergence of sporadic PD. Similar to this, in the case of FTDP, an increase in the accumulation of p-tau is brought about by a mutation in the gene coding for microtubule associated protein (MAPT). Additionally, p-tau has been connected to mutations in the LRRK2 gene. Despite having a strong association with AD, NFTs can co-localize with SNCA in LB and have a significant part in the DA-neuronal architecture's destabilization, which ultimately resulted in sluggish aging and demise of neurons.[19]

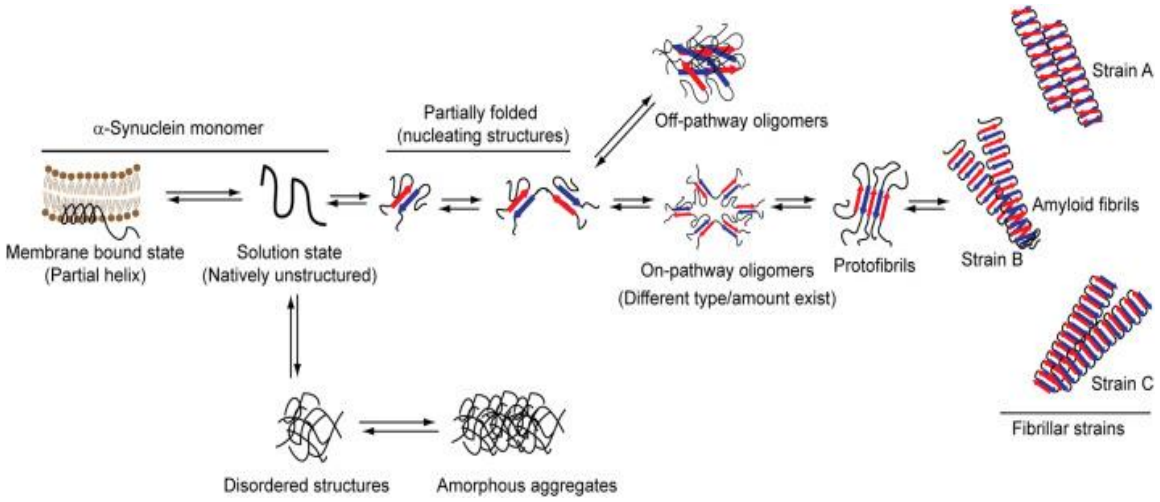

Figure Number 3: Diagrammatic representation of the steps leading to the accumulation of SNCA. A major factor in the loss of DA neurons in Parkinson's disease (PD) is the misfolding of natural SNCA under stress, which results in the deposition of oligomers, tiny aggregates, or fibrils.

PD's Role for Mutations

Numerous recent studies show that 5–10% of late-onset forms of PD are related to genetic factors, including the identification of gene mutations in familial or inherited forms of the disease. SNCA, parkin, and PINK1 are the most often found genes linked to Parkinson's disease. Research and medical data indicate that there are five distinct chromosomes (5, 6, 8, 9, and) that are associated with a higher risk of Parkinson's disease (PD). The Parkingene, for instance, is a chromosome that has genes linked to the early development of Parkinson's disease. Additionally, certain patients with Parkinson's disease who do not react to L-DOPA therapy have particular genes on chromosomes. In a similar vein, the tau gene lies next to the FTDP chromosome, which is connected to the late-onset PD. Furthermore, genes on chromosomes X, 1, 2, and ubiquitin carboxyl-terminal hydroxylase (UCH-L1) play important roles in the etiology of Parkinson's disease (PD) in some families.[20]

(i) Parkin. Parkinson’s is a significant protein linked to protein clearance processes, including the ubiquitin proteasome system, which aids in the breakdown of misfolded proteins within cells. As an E3 ubiquitin ligase, parkin can bind covalently to ubiquitin on a variety of misfolded protein substrates to facilitate the destruction of those proteins. Parkin may create LB inclusions and has also been co-localized with SNCA. On the other hand, misfolded amyloid proteins may aggregate within SNpc as a result of parkin mutations. Neurons in the midbrain locus coeruleus are lost in parkin-deficient animals and in

individuals with idiopathic Parkinson's disease (PD). Additionally, parkin mutations have the potential to dramatically reduce ubiquitin-ligase enzymatic activity in the SNpc, which can significantly slow down the proteasomal breakdown process in the event of autosomal recessive juvenile Parkinsonism. Furthermore, parkin plays a role in controlling the release of DA from SNpc.[21]

(ii) DJ-1 (PARK7). DJ-1 is a 189 amino acid dimer that is found in the cytoplasm, nucleus, and mitochondria. It has been associated with Parkinson's disease (PD) that manifests early. Numerous in vitro studies have demonstrated its neuroprotective properties, which include transcriptional regulation, antioxidant action, chaperone and protease activity, and modulation of the activity of particular genes essential to cell survival (PI3 K/Akt pathway). Mice lacking DJ-1 have impaired locomotion, reduced D2 type DA receptor activation, and increased MPTP sensitivity. Similarly, point mutations and DJ-1 deletions lead to the development of autosomal recessive Parkinson's disease. Furthermore, DJ-1 has been shown to co-localize with SNCA and p-tau, suggesting that DJ-1 may be important in tauopathies and synucleinopathies. Moreover, DJ-1 can bind to a number of chaperones, such as misfolded SNCA and the carboxy-terminus of HSP70 interacting protein (CHIP), as well as mitochondrial HSP70/mortalin/Grp75. In order to sustain TH levels in DA neurons of SNpc, DJ-1 furthermore regulates the expression of the human TH gene by removing the transcriptional repressor poly-pyrimidine tract binding protein-associated splicing factor (PSF) from the human TH gene promoter.

(iii) (Dardarin) LRRK2/PARK8. The PARK8 gene encodes the 268 kDa multi-domain protein known as leucine-rich repeat kinase (LRRK2). Late-onset Parkinson's disease has been associated with several point mutations on the PARK8 gene. Several point mutations in PARK8, with severe DA neurodegeneration, with or without the presence of LB aggregation, have been found in post-mortem tissue from patients with Parkinson's disease. Furthermore, mutations in the LRRK2 gene may be connected to the p-tau pathology found in the post-mortem brains of Parkinson's disease patients.[22]

(iv) PARK3, PARK9, PARK10, and PARK11Park3. PARK-3, 9-, 10-, and 11-gene mutations are also linked to familial Parkinson's disease. For instance, a mutation in the PARK3 gene is associated with the emergence of late-stage SPD.

(v) Mutation of the glucosecerebrosidase (GBA) gene. One of the most prevalent genetic risk factors for Parkinsonism is thought to be GBA. Velayati et al. have demonstrated that GBA gene mutations are linked to both LBD and Parkinson's disease development. The GBA mutations are linked to changes in lipid levels, which can result in autophagy lysosomal dysfunction and lysosomal storage disorder, which can cause synucleinopathies. The neuroprotective ganglioside (GM1) and the toxic gangliosides (GD3 and GT3 series) are linked to each other, and a mutation in GM1 synthase or an upregulation of ganglioside-3 synthase (GD3S) can cause neurodegeneration in the SNpc in MPTP-lesion mice.[23]

Environmental pollutants' impact on Parkinson's disease

Farmers are using a variety of pesticides, sometimes indiscriminately, to increase crop yields as a result of recent yield-boosting developments in the fertilizer and agriculture sectors. The development of SP has been attributed in part to exposure to such environmental chemicals (pesticides, herbicides, fungicides, insecticides, etc.). Importantly, exposure to those toxins—either by direct touch or by drinking water—makes farmers and residents in rural areas susceptible to Parkinson's disease. In addition, a lot of people get exposed to viruses, bacteria, or illicit street substances like synthetic heroin (MPTP, also known as 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine), which can cause SPD. When MPTP is introduced into the cell, the true poisonous metabolite, MPP+, is produced. It has the ability to assault DA-neurons in SNpc via DAT, resulting in Parkinsonism. MPTP is currently commonly utilized to induce severe, permanent parkinsonian symptoms in animal models of Parkinson's disease (PD) because of this capability. A number of environmental toxins, including paraquat, maneb, zineb, nabam, thiram, ziram, and rotenone, have structural similarities with MPTP and have the potential to cause Parkinsonism in animals. For instance, five weeks after receiving an MPTP injection (25 mg/kg BW) for five days, mice in one of our studies displayed an 80% decrease of TH-immunoreactivity in the SNpc, indicating a significant loss of DA-neurons in that region. Additionally, we noticed that TH-positive DA-fibers were sparser in the striatum, which implies that the DA fibers in the striatum became decreased as a result of the loss of DA neurons in SNPc. Similarly, giving animals an injection of 6 hydroxydopamine (6-OHDA) in the striatum can cause symptoms similar to Parkinson's disease. Similar to MPTP exposure, rotenone is another well-known pesticide ingredient that degenerates DA neurons in SNPc as a result of energy failure.[24] According to a number of studies, the majority of environmental pollutants have the ability to interfere with the mitochondrial electron transport system and limit complex-I function. This can ultimately increase the formation of

free radicals, which can result in oxidative stress. Despite the fact that numerous researchers have created numerous animal models of Parkinson's disease (PD) utilizing environmental toxins, none of them showed the main symptoms of PD. resembling bradykinesia or resting tremor. Furthermore, they are unable to precisely summarize the mechanisms behind DA neuronal loss. Moreover, these poisons can trigger abrupt or fast cell death, unlike gradual neurodegeneration found in PD. In addition, most medicines utilized to protect against the neurotoxicity produced by these environ mental toxins in animal models are difficult to translate into successful human therapy. As such, choosing a toxin to create an animal model of Parkinson's disease is a difficult undertaking.[25]

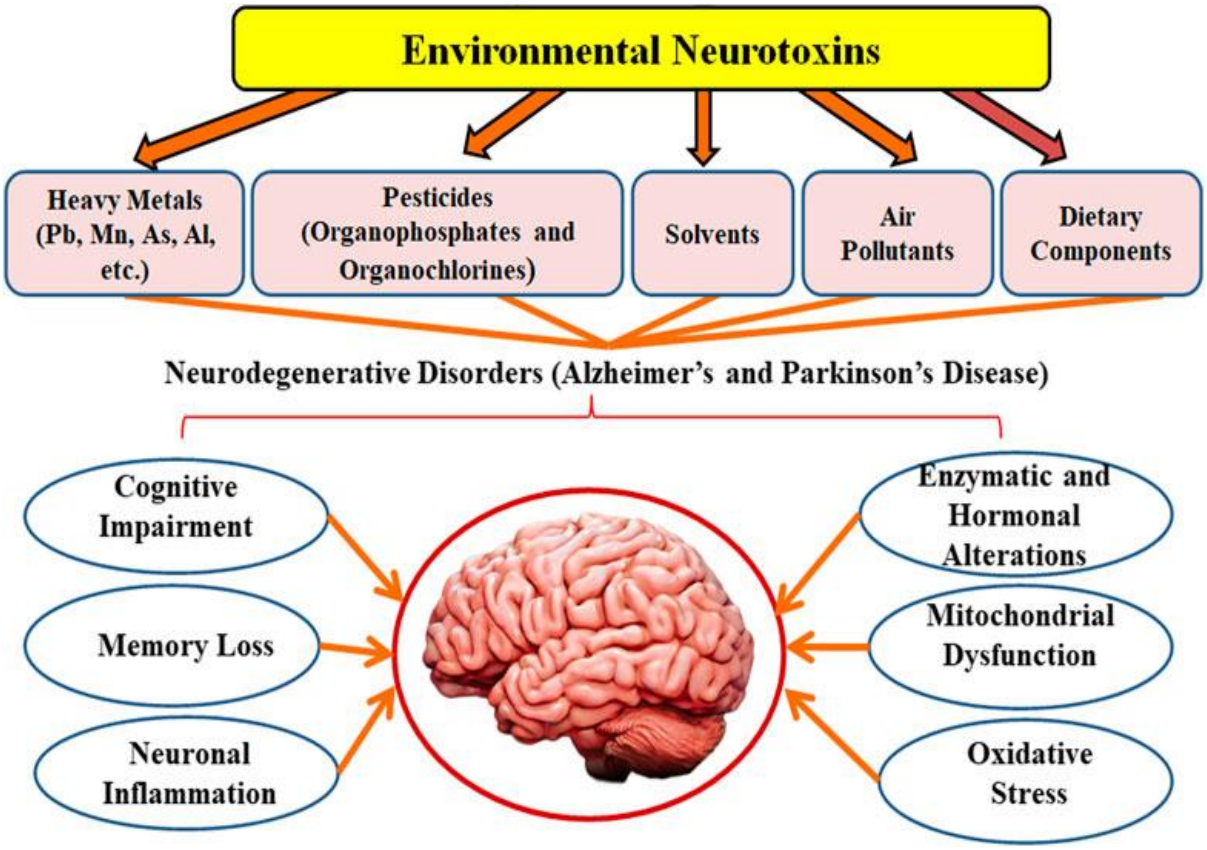

Figure Number 4: Role of environmental toxins in Parkinson's disease.

Various environmental pollutants linked to Parkinsonism and neurodegeneration

Toxins	Use	Mode of action	Effects on nervous system
Rotenone	Herbicide	Stop the flow of electron	Parkinsonism
MPTP	Insecticide, pesticide	disrupt the mechanism That transports electrons within Mitochondria.	Parkinson's like symptoms
Paraquat	Herbicide	disrupt the flow of electrons,	Stress caused by oxidation
Maneb	fungicide	photosynthesis	Parkinson's like symptoms
Zineb	Insecticide	disrupts glucocorticoids	fatigue, lightheadedness, and

Ziram	Insecticide	metabolism converted to carbon Neurotoxin disulphide.	Convulsions, weariness slurred speech, headache, weakness, unconsciousness. Long-term inhalation disrupts the nervous system and eyes.
Thirum and Nabam	Insecticide fungicide	Not sure Not sure	headaches, vertigo, Exhaustion, sleepiness, Disorientation. convulsion, vertigo, and Disorientation.[26]

NEURO INFLAMMATION IN PARKINSON'S DISEASE

One of the main cell types in the central nervous system (CNS) that contributes to inflammatory reactions are microglia. There is growing evidence that microglia exhibit two distinct activation phenotypes: the pro-inflammatory M1 phenotype and the anti-inflammatory M2 phenotype. The production of various arrays of cytokines characterizes these distinct activation stages of microglia. It has been shown that in microglia, treatment with LPS/IFN-γ causes M1 activation, but treatment with IL-4/IL-13 causes M2 activation. Pro-inflammatory cytokines such as TNF-α, IL-1β, IL-6, and IL-12, as well as other cytotoxic molecules like superoxide, NO, and reactive oxygen species (ROS), are produced during classical M1 activation of microglia, which contributes to the amplification of the pro-inflammatory responses during injuries and infections.[27] On the other hand, M2 microglia suppress the immune system by opposing the traditional M1 microglia and encouraging tissue healing. Numerous cytokines with anti-inflammatory properties, including IL-4, IL-13, IL-10, and TGF-β, are produced by M2 microglia. Microglia exhibit distinct activation forms that can be identified by their unique pattern of gene expression. In mouse M2 phase microglia, for instance, Arg1, FIZZ1 (also called RELM-α), Chi3l3 (also called YM1), and CD206 were expressed. Since the levels of Arg1, FIZZ1, and Chi3l3 are markedly increased in primary cultured microglia or the striatal and frontal cortical regions of the mouse brain following IL-4 stimulation, it is possible that cytokines influence the expression of these genes. What elements influence the phenotype of M1/M2 microglia in Parkinson's disease? In animal models of Parkinson's disease, misfolded proteins and environmental pollutants cause microglia to become activated and adopt an M1 phenotype. Chronic MPTP treatment causes CD206 expression to gradually decline, which may indicate that M2phase microglia activation is downregulated as Parkinson's disease progresses. On the other hand, IL-4 therapy increases the expression of histone H3K27me3 demethylase (Jmjd3) in microglia, which is connected to the control of chromosome epigenetic modification and plays a role in a number of human illnesses.[28] Jmjd3 is crucial for M2 microglia polarization, as evidenced

by the marked down-regulation of M2 marker gene expression levels in the N9 microglia cell line following Jmjd3 knockdown. These genes include Arg1 and CD206.

By reversing the M2 activation of microglia, Jmjd3 knockdown in vivo exacerbates the loss of DA neurons in the SNpc of the MPTP-induced animal PD model. Conditioned medium (CM) derived from M1 phase N9 microglia causes DA neurons to die more frequently, whereas CM mixture derived from M1 and M2 cells counteracts the neurotoxicity caused by the M1-CM. Previous studies in different models showed that most activated microglia express genes related to M2 in the initial stages after damage. However, in subsequent stages, M1 signature genes gradually take center stage.[29] These intriguing findings imply that, in Parkinson's disease, it's critical to maintain a balance between various microglia activation phenotypes. Controlling the shift in microglia activation statuses seems to be a viable way to halt the progression of Parkinson's disease. Present studies indicate that M1 and M2 play distinct roles in the pathophysiology of Parkinson's disease (PD) in animal models; nonetheless, Patients' results are not comparable. Research on this topic should be warranted for future work.[30]

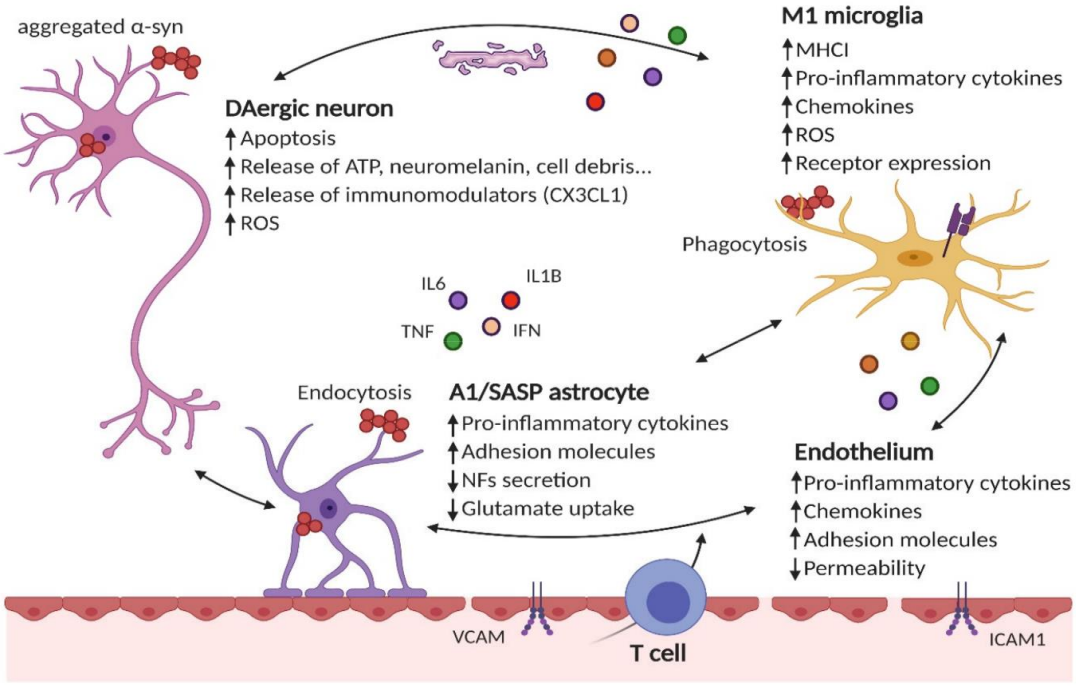

Figure Number 5: An illustration of the pathophysiological causes of inflammation in Parkinson's disease. Pathological events such as protein aggregation, gene mutations, environmental variables, and cytokines secreted from infiltrating T cells cause microglia in Parkinson's disease (PD) to adopt an activated M1 phenotype. M1 microglia's pro-

inflammatory mediators stimulate astrocytes, which increases the production of pro inflammatory substances, nitric oxide, and superoxide radical, which in turn causes DA neurons to degenerate. Degenerative DA neurons emit chemicals that can further activate glia and intensify the inflammatory response. A subpopulation of microglia may develop into an activated M2 phenotype at a specific stage of Parkinson's disease (PD), releasing anti-inflammatory molecules like TGF-β and having a neuroprotective effect.[31]

PD clinical diagnosis

Parkinson's disease (PD) is characterized by bradykinesia, stiffness, and rest tremor. Maybe not all of these are here. While postural instability may be present, progressive supranuclear palsy (PSP) is more likely to be indicated by early postural instability in the past, especially in cases where there has been a history of falls. When PD occurs, the clinical symptoms are typically asymmetrical. Although the clinical diagnosis may seem clear-cut in most cases, it is important to remember that up to 25% of PD patients diagnosed by general neurologists had a different diagnosis revealed in post-mortem examinations.[32] Notably, individuals identified in expert movement disorder clinics have significantly lower rates of diagnostic error12, which supports the recommendation that patients be referred to movement disorder specialists as soon as possible. Numerous clinical standards have been developed. There are also more clinical indicators that are noteworthy. Micrographia frequently manifests early as a shift in handwriting and a decrease in facial expression. An early and helpful diagnostic sign is also the loss of arm swing on one side. It doesn't appear like a glabellar tap is very sensitive or specific. It is worthwhile to inquire about a diminished sense of smell, though, as this could be among the initial signs of early Parkinson's disease. Thirteen Hypophonia, salivary drooling (from decreased swallowing), and impaired postural reflexes may occur as the condition progresses.[33]

Step 1: A parkinsonian syndrome diagnosis

Bradykinesia, which is characterized by a gradual decrease in the speed and amplitude of repeating motions accompanied by a slow start to voluntary movement, and at least one of the following conditions.

(i) Rigidity of the muscles;

(ii) Tremor at rest of 4-6 Hz; and

(iii) Instability of the posture not resulting from basic problems with vision, vestibular, cerebellar, or proprioceptive function[34]

Step 2: PD exclusion standards

(i) A history of several strokes accompanied by a progressive development of parkinsonian trait.

(ii) A history of concussions to the head;

(iii) A history of conclusive encephalitis;

(iv) Ocular emergencies.

(v) Therapy with neuroleptics as soon as symptoms appear.

(vi) Multiple relatives afflicted.

(vii) Long-lasting remission.

(viii) After three years, strictly unilateral traits.

(ix) Palsy of supranuclear gaze.

(x) Brainstem indications.

(xi) Initial severe autonomic disturbance.

(xii) Memory, language, and praxis abnormalities accompany early, severe dementia.

(xiii) The sign of Babinski.

(xiv) CT scan evidence of a brain tumor or communicative hydrocephalus.

(xv) Negative reaction to high levodopa dosages (if malabsorption is not present.[35]

Step 3: Supportive criteria for Parkinson's disease (three or more needed for a definitive diagnosis of PD)

(i) One-sided onset.

(ii) Presence of rest tremor.

(iii) Progressive disorder.

(iv) Persistent asymmetry that mostly affects one side of the start.

(v) Excellent levodopa response (70–100%).

(vi) Severe chorea brought on by levodopa.

(vii) Response to levodopa over at least five years.

(viii) A minimum of ten years of clinical training.

As the condition worsens, non-motor problems frequently become more problematic. Asking about depression symptoms, which affect roughly 40% of PD patients, is beneficial.[36]

MEDICATIONS FOR PARKINSON'S DISEASE

While there are several generic medications available to lessen the pathogenesis of Parkinson's disease, choosing the appropriate dose is the most important component. Because

medications may take some time to take effect in the patient's body, a doctor will always evaluate the medication's impact on the patient's day-to-day functioning during a suggested course of treatment. Infusion or microinjection techniques have made it possible to infuse several neuroactive chemicals into the parts of the brain affected by Parkinson's disease. At the moment, there are two types of PD medicines available: medicines that are dopaminergic; medicines that are not dopaminergic.[37]

Different phases in which Parkinson's disease symptoms evolve, as explained by Hoehn and Yahr.

Stage I: One-sided signs and symptoms; limb tremor; slight alterations in posture, gait, and expression and expression.

Stage II: symptoms include minor impairment, both sides, and altered posture and gait.

Stage III: Generalized dysfunctions; early deterioration of equilibrium when walking or slipping; slowing down of body movements.

Stage IV: Severe symptoms, stiffness and bradykinesia, restricted ability to walk, inability to live alone, and possibly less tremor than in an earlier stage.

Stage V: Cachectic stage; total invalidism; unable to walk or stand; in need of continuous nursing care.[38]

Dopaminergic drugs

Levodopa (L-DOPA). In order to restore DA levels, doctors typically prescribe DA-drugs to patients with Parkinson's disease. Since dopamine (DA) cannot cross the blood-brain barrier on its own, levodopa (L-3,4dihydroxyphenylalanine/L-DOPA) and other DA precursors are frequently administered. While L-DOPA can effectively lessen "resting-tremors" and other basic symptoms, it cannot stop the progression of Parkinson's disease (PD) or preserve or replace damaged DA neurons. In addition, it could result in low blood pressure, nausea, vomiting, restlessness, drowsiness, or an abrupt start to sleep. Additionally, doctors commonly prescribe carbidopa, which prolongs the therapeutic impact when given in conjugation with L-DOPA, because L-DOPA converts quickly to DA, lowering its efficacy when it reaches the target area.[39]

MAO-B inhibitors. The catalytic enzyme monoamine oxidase-B (MAO-B), whose level is elevated in the PD brain, may be the cause of the decrease in DA levels in PD. As a result, blocking MAO-B is an effective way to keep DA levels in the PD brain stable. The most widely used and well-tolerated MAO-B inhibitors are rasagiline (L-deprenyl) and Selegiline

.When used with L-DOPA, these drugs can prolong the effects of L-DOPA for up to a year or more. While there have been a number of negative effects associated with these medications, they appear to be effective in either restoring cell function or delaying the loss of dopaminergic neurons in Parkinson's disease.[40]

Inhibitors of COMT. The enzyme catechol-O-methyl transferase (COMT) can further catalyze the conversion of dihydroxy phenyl acetate, which is produced when MAO breaks down DA, to homovanillic acid.

Since COMT is indirectly responsible for the breakdown of DA, inhibiting COMT may be an additional strategy to treat PD and restore DA. Entacapone and Tolcapone are two typical COMT inhibitors that prolong the effects of L DOPA by inhibiting the breakdown of docosahexamine (DA). These medications can also lessen a patient's susceptibility to L DOPA and have less adverse effects.[41]

Agonists of dopamine. These medications work best in the early stages of Parkinson's disease (PD) and can raise dopamine (DA) levels in the brain. To extend the half-life of L-DOPA in the last stages of Parkinson's disease, they can also be mixed with it. L-DOPA is often more successful than Pramipexole and Ropinirole in managing rigidity and bradykinesia in people with Parkinson's disease (PD). These DA agonists are frequently used to treat PD patients. Regretfully, these medications may cause a number of negative effects that are comparable to those of L-DOPA.[42]

Non dopaminergic medications

Anti-cholinergic chemicals, norepinephrine (NE), compounds related to serotonergic and muscarinic receptors, and antiviral medications are examples of non-dopaminergic medications.

medication that is anticholinergic. One of the most significant excitatory neurotransmitters in the brain is ACh, which has been shown to be reduced in a number of different brain regions in Parkinson's disease patients. Because of decreased DA levels, which result in less inhibitory action in the brain, ACh-induced excitation can persist in Parkinson's disease (PD) until it reaches the point of over excitation. Anticholinergic medications may therefore be beneficial. Anti-ACh medications can help individuals with Parkinson's disease (PD) have less tremors and stiffness in their muscles, but only approximately 50% of patients experience

any relief, and even then, it is only temporary, with just 30% of patients exhibiting any clinical improvements. In addition, anti-ACh medications have a number of adverse effects.[43]

Other drugs

Antidepressants can be used to treat non-motor symptoms including anxiety and depression. Although it has certain negative effects, benzodiazepines are among the most often prescribed medications for treating anxiety in people with Parkinson's disease. Similarly, clozapine is recommended to treat Parkinson's disease dyskinesia; nevertheless, it can have adverse effects, including agranulocytosis.[44]

FUTURE DIRECTIONS FOR PD RESEARCH AND THERAPEUTIC DEVELOPMENTS

Our in-depth study of animals has allowed us to solve a number of important issues in this intricate field. Nevertheless, no animal model can perfectly replicate the neuropathological alterations and behavioral abnormalities seen in PD patients. Thus, a variety of approaches can be used to mimic the symptoms of Parkinson's disease in humans and address specific research questions. These include: (i) creating a novel animal model, which can be created by combining two or more animal models, such as transgenic (for genetic effects) and sporadic (for toxin effects); (ii) employing a variety of non-DA medications, such as α2-adrenergic antagonists, serotonergic, and adenosine A2a antagonists, which may have positive effects on the later stages of Parkinson's disease motor symptoms[45] (iii) the creation of innovative formulas for levodopa/carbidopa medications (such as IPX066, XP21279, and Opicapone), as well as MAO-inhibitors (such as safinamide: 100–200 mg/day), which have a positive clinical impact on patients with both early and advanced Parkinson's disease (PD) both immediately and over time without causing adverse effects like dyskinesia or depression; (iv) Using novel pharmaceutical molecules to target ALP and UPS may be a promising approach for treating Parkinson's disease (PD); (v) creating transplantation therapies using unique DA neurons derived from induced pluripotent stem cells or induced neuronal stem cells; (vi) using micro-RNA or Si-RNA to block the mRNA of misfolded protein aggregates; and (vii) using cutting-edge gene editing methods (like CRISP-Cas9) to correct mutated genes linked to Parkinson's disease (PD).[46] Drugs to treat Parkinson's disease are continuously being developed and some of them are already helping PD patients live better lives. Before safe and successful gene therapy is applied to treat Parkinson's disease (PD), a number of concerns

must be resolved. Developing safe marker genes, choosing innovative vectors carefully, determining which precise genes to employ for rectification, and developing modulators of precise gene expression in the central nervous system are a few of these issues.[47]

CONCLUSIONS

Because of the growing number of elderly people, there is a steady rise in Parkinson's disease instances. The financial and psychological effects of Parkinson's disease (PD) on the general public's health as well as the relatives and friends of people who have the illness are profound. Prognosis or early detection will therefore be essential for identifying persons who are at risk of contracting this illness. There are a number of therapies available, but none of them is very good in lowering the death of dopaminergic neurons and raising dopamine levels in the striatum In addition, a few of the medications are pricey and have harmful side effects. In an effort to treat this illness, scientists have recently presented numerous intriguing substitute techniques, including gene therapy and stem cell transplantation. Before they can be utilized in PD clinical trials, safety and efficacy concerns must be sufficiently resolved, as the majority of these novel therapeutic approaches are currently being researched and have only been tested in animal models. However, the novel therapeutic strategies discussed in this study offer considerable hope that PD therapies will soon be available.

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