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A Review on Parkinson's Disease: It's Pathogenesis, Pathways and Prevention

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ABSTRACT

There are several most prevalent diseases related to central nervous system such as Alzheimer brain tumor, hydrocephalus, pseudotumor cerebri. The present study was carried on Parkinson's disease. It is the most common diseases among several neuron related diseases. Parkinson's disease (PD) is a slowly progressive, neurodegenerative, age-related, second most common disorder of the central nervous system of the brain after Alzheimer's disease. In this disease, the motor neurons system is primarily affected by a loss of chemical messenger dopamine (DA), presence of Lewy bodies (LBs) and Lewy neurites (LN) that contain aggregates of alpha synuclein protein. During Parkinson's disease, cell loss occurs within the areas of the midbrain called substantial nigra and also affects the ventral component of the pars compacts. In this study, we focused on the study of the symptoms, cellular dysfunction and pathways that are involved in PD. Till date, there are various therapeutic approaches having been developed for the treatment of advanced PD comprising Pharmacotherapy, neurotrophic factors, surgical procedures such as DBS, cell-based therapies and gene therapies. Thus, here a detailed knowledge of genetic basis of PD will provide a basis for further studies and help researchers to understand the basic mechanism underlying the disease.

INTRODUCTION

Parkinson's disease (PD) is a neurodegenerative disorder that affects predominately dopamine-producing neurons (dopaminergic) in a specific area of the brain called substantia nigra. These nerve cells make an important chemical called dopamine. A chemical responsible for transmitted messages to part of the brain that coordinate muscle movement. The discovery of PD genes has led to the hypothesis that the misfolding of proteins and dysfunction of the ubiquitin-proteasome pathway are pivotal to PD pathogenesis. Parkinson's disease mainly affects adults older than 60years. It affects at least 500,000 people in the United States, according to the National Institute of Neurological Disorders and Stroke. Approximately 60,000 new cases are reported in the United States each year. Though, the prevalence of PD in India is less common than to other countries. About 1% of people above of 65 years old and 4-5% of people above of 85 years are affected by this disease in India. [1].

HISTORY OF PD

Parkinson's disease was first introduced in the year 1817 by James Parkinson in "An essay on the Shaking Palsy" and it was reported in 1893 that the symptoms of PD were attributable to severe degeneration of dopaminergic neurons in the substantia nigra pars compacta. He also found that it was the loss of neurons in the substantia nigra pars compacta (SNPc). He described the core clinical features of the second most common age-related neurodegenerative Parkinson's disease after Alzheimer's disease (AD). Jean-Martin Charcot (1825-1893) studies in between 1868 and 1881 that are described today by medical historians as a "landmark in the understanding of Parkinson's disease". He also clearly defined and explained the difference between rigidity, weakness and bradykinesia slowness in the execution of movement). Frederic Lewy (1885-1950) - a prominent american neurologist is best known for the discovery of Lewy bodies, characteristic indicators of dementia with Lewy Bodies and Parkinson's disease. Konstantin Nikolaevitch Tretiakoff (1892-1958) was the first to link this anatomic structure with Parkinson's disease and described the degeneration of the substantia nigra in cases of Parkinson's. Rolf Hassler (1914-1984) made an important discovery in the treatment of Parkinson's disease. He wrote that autopsies of Parkinson's patients showed that the most affected part of the brain was the substantia nigra pars pallidus, which lost many neurons and had an abundant accumulation of Lewy bodies. It was followed by Arvid Carlsson's in 1958 that led to the discovery of dopamine (DA) in the

mammalian brain. PD affects approximately 1.5 million people in the United States. However, the knowledge about this disease has been present in India since ancient times.

ETIOLOGY OF DISEASE

PD is involved in circumscribed portions of the central, peripheral, and enteric nervous systems (CNS, PNS and ENS) [2,3,4]. It mainly affects the motor system that controls the movement. It belongs to a group of conditions called movement disorders that leads to a variety of abnormal body movements having neurological basis.

Several pathways are involved in Parkinson's disease that are linked to the dysfunctions in the protein degradation systems such as ubiquitin-preoteasome system (UPS) and autophagy, mitochondrial dysfunction, oxidative and nitrative stress and inflammation.

Several causes of Parkinson's Disease are genetics (several genes including such as Ubiquitin Carboxyl-Terminal Hydrolase L1 (UCH-L1), PARK5, glutathione S transferase omega-1 (GSTO-1), tau and FGF2 gene, PARK3, PARK9, PARK10 and PARK11 etc), environment factors (includes exposure to toxic such as herbicides, pesticides, insecticides that interfere with the activity of mitochondrial complex-I and agent orange, drinking well water and consumption of manganese), protein aggregation, over stimulation of nerve cells, loss of dopamine, age and gender(Men are more susceptible than women), occupations(people who are in contacts of exposure of toxic chemicals or in profession of welding, agriculture, and industrial work), inflammation in brain, air pollution, nicotine, REM sleep disorder (rapid eye movement) and some reheated cooking oils containing aldehydes .While chemicals include 6-Hydroxydopamine, MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyrimidine).

Syndromes including in this conditions are cerebral palsy, ataxia, and Tourette syndrome. While early symptoms of PD includes small handwritings that is a sudden change in the size of handwriting. Some motor and non-motor symptoms are also known to be associated with PD. The motor symptoms include resting, tremor, rigidity, bradykinesia (slowness of movement) and postural instability [5] while non-motor symptoms include depression, emotional changes, dysphagia, urinary problems, skin problems, pain, sleep disorders, sexual dysfunction etc [6,7]. Exposure of humans to (1-methyl-4-phenyl-1,2,3,6-tetrahydropyrimidine) causes a syndrome that mimics the core neurological symptoms and affected dopaminergic neurodegeneration of PD. MPTP (1-methyl-4-phenyl-1,2,3,6-

tetrahydropyrimidine) toxicity have been studied in mice and considered as the model animal of PD.

Parkinson's disease can be prevented by surgery incudes pallidotomy and deep brain stimulation (DBS), improving diet, exercises, by regular uptake of Curcumin - an ingredient found in the spice turmeric, anthocyanins, a subclass of flavonoids, consumption of caffeine, by inhibition of the aggregation of protein that is Lewis bodies, by drug therapies (drugs including glial cell line-derived neurotrophic factor (GDNF that protect dopamine neurons), levodopa , dopamine agonists, apomorphine, anticholinergics, anticholinergics and COMT (Catechol-O-methyltransferase) inhibitors that inhibits the action of catechol-O-methyl transferase.

The abundance of guidelines for PD diagnosis is reflective of the difficulty in diagnosing this condition. One relatively straightforward list of research criteria for probable PD includes:

1) Evidence of disease progression

2) Presence of at least two of the three cardinal features of parkinsonism (tremor, rigidity, bradykinesia)

3) Presence of at least two of the following:

a.) Marked response to L-dopa (functional improvement or dyskinesia)

b.) Asymmetry of signs

c.) Asymmetry at onset

4) Absence of clinical features of alternative diagnosis

5) Absence of etiology known to cause similar features

Assessment of PD Severity includes

Many clinical investigators use different scoring scales to assess the severity of PD symptoms, making it difficult to compare results across studies. The most common scale used to assess PD severity is the Unified Parkinson's Disease Rating Scale (UPDRS), which has superceded numerous other scales, including Hoehn & Yahr Disability Scale (H&Y), Schwab & England (S&E) Activities of Daily Living (ADL) scale, Webster scale, Columbia

University Rating Scale (CURS), and Northwestern University Disability Scale (NUDS). Appendix A describes the major scales used to assess PD severity. In the UPDRS, a rating tool that was developed in 1984, points are assigned for a comprehensive list of PD symptoms. 53, 54, 55 Patients may receive a total of 199 points, with 0 representing no disability, and 199 representing total disability. The total score is composed of four major subscales: I) Mutation, Behavior, and Mood (range 0-16),

II) ADL (range 0-104),

III) Motor Exam (range 0-56), and

IV) Complications of therapy over the past week (range 0-23).

Each of these subscales is broken down into further subscales, which range from 0 (normal) to 4 (maximum severity). Each UPDRS score may be reported in the "off" and "on" state, which refer to presence or absence of L-dopa effectiveness. Practically-defined "off" scores are measured approximately 12 hours after the last dose of L-dopa, although in actual clinical practice, off scores often indicate periods when the patients feel their medication is not working. On scores are measured shortly after a dose, or when patients feel their medication is working. The UPDRS scales are validated tools that are useful in following the progression of disease and response to interventions.

The H&Y scale divides patients into stages, based on their levels of clinical disability. Stage 0 patients have no signs of disease. Stage I patients have unilateral involvement, with minimal or no functional impairment. Stage II patients have bilateral or midline involvement, without balance impairment. Stage III patients have impaired equilibrium, unsteadiness, and significant slowing of body movements. Stage IV patients have severe symptoms, are still able to walk and stand unassisted, but are extremely incapacitated and unable to live alone. Stage V patients are confined to bed or wheelchair and require constant nursing care. The S&E ADL scale has ratings from 0 to 100 percent, where 0 is bedridden with no swallowing, bladder, or bowel function, and 100 percent is completely independent.

PATHOLOGY OF PARKINSON'S DISEASE

PD is a chronic and progressive, neurodegenerative disorder characterized pathologically by the loss of 50–70% of the dopaminergic neurons in the SNPc and the presence of LBs and

LN that contain aggregates of α -synuclein protein. The unfolded protein α-synuclein is present in erythrocytes and platelets. It is a predominantly neuronal protein that matures into human nerve cell [8]. It is produced in the nerve cell soma and is redistributed in the axonal compartment and ultimately resides in presynaptic terminals, where it contributes to neurotransmission and synaptic homeostasis [9, 10]. Due to loss of dopamine agonists (DA) in the neurons of region, they are not able to transfer messages from brain to any parts of human body. Apart from nigral dopaminergic neuronal degeneration, loss of noradrenaline neurones of the LC, cholinergic neurones of the NBM, serotonin neurones of the dorsal raphe nuclei (+RN), degeneration of neurones in the olfactory system, dorsal motor nucleus of the vagus (DMNV) and the PNS also occurred in Parkinson's disease [11, 12, 13]. Degeneration of the neurons other brain regions has been suggested to be the cause of non-motor symptoms of Parkinson's disease. For example, depression that is related to the loss of noradrenergic transmission in the limbic system, whereas dementia has been linked to the destruction of the cholinergic system [14,15]. While some pathological symptoms of Parkinson's disease are defined as by the formation of α-synuclein immunoreactive inclusion bodies [16] that develops in a susceptible neuronal types within circumscribed portions of the CNS (Central nervous system), PNS, and ENS [17,18]. The inclusions occur in the form of spherical LBs in cell stomata [19]. As elongated spindle-shaped or thread-like LNs in axons and dendrites as pale bodies and sometimes as particulate (granular, dot-like, punctate) aggregates [20]. The etiology and pathogenesis is depicted in Fig 1.

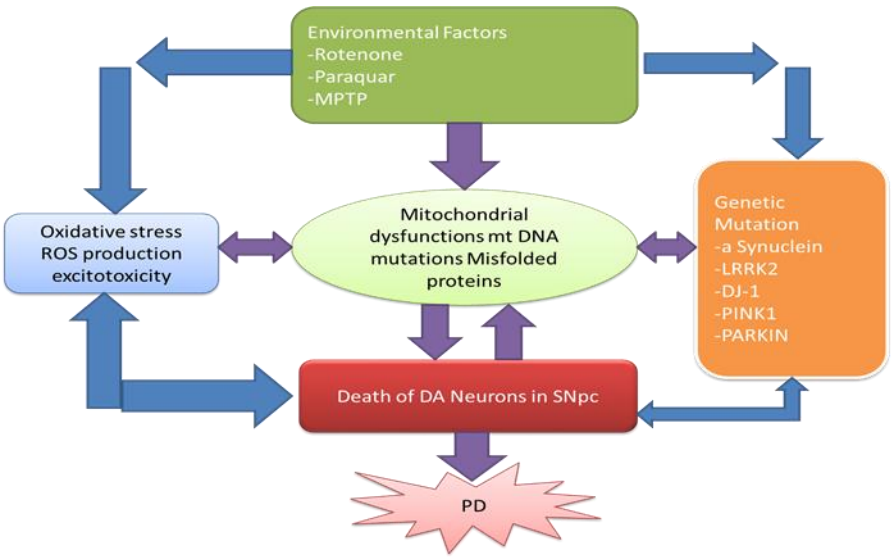

Fig 1: Etiology and pathogenesis of Parkinson's disease

STAGES OF PARKINSON DISEASE

There are five stages of Parkinson's disease that are described as below-

Stage I: Involvement Only, Usually With Minimal or No Functional Impairment

The patient has tremor, rigidity, slowness and paucity of movement, or poor condition in the arm and/or legs on one side of the body. Occasionally one side of the face is involved, producing an asymmetry of expression that may look very like the effects of a mild stroke or Bell's palsy.

Stage II: Bilateral or Midline Involvement, Without Impairment of Balance

Months or years later similar symptoms and signs are noticed on the opposite side of the body, or other signs appear in "midline" what physicians call "Axial" signs. These may include: bilateral loss of facial expression (masking); decreased blinking; speech abnormalities; soft voice, monotony, fading volume after starting to speak loudly, slurring, stiffness (rigidity) of truncal muscles making the patient appear awkward and stiff or resulting in neck and back pain; postural abnormalities causing stooping, generalized slowness.

Stage III: First Signs of Impaired Righting Reflexes

This is Evident As The Patient Turns or Is Demonstrated When He or She Is Pushed From Standing Equilibrium With The Feet Together And Eyes Closed**.** Loss of balance, with the inability to make the rapid, automatic and involuntary movements necessary to protect against falling.

Stage IV: In this stage, patient is unable to lead an independent life because of the need for help with some activities of daily living. It is this inability to live alone which marks the transition from Stage III to Stage IV.

Stage V: Confinement to Bed or Wheelchair Unless Aided

The patient may exhibit inability to arise from a chair or get out of bed without help; a tendency to fall when standing or turning; freezing, stumbling or pulsion when walking.

PARKINSON'S SYMPTOMS

The symptoms of Parkinson disease are divided into two categories: motor (Fig 2) and non motor symptoms (Fig 3) and are shown in table 1.

Table 1: Motor and Nonmotor symptoms of Parkinson's disease

S.No.	Motor symptoms	Non-motor symptoms
1.	Tremor, bradykinesia, rigidity, postural instability	Cognitive impairment, bradyphrenia, tip-of-the-tongue (word finding) phenomenon
2.	Hypomania, Dysarthria, dysphagia, sialorrhoea	Depression, apathy, anhedonia, fatigue, other behavioral and psychiatric problems
3.	Decreased arm swing, shuffling gait, festination difficulty arising from chair, turning in bed	Sensory symptoms: anosmia, ageusia, pain (shoulder, back), paresthesias
4.	Micrographia, cutting food, feeding, hygiene, slow activities of daily living	Dysautonomia (orthostatic hypotension, constipation, urinary and sexual dysfunction, abnormal sweating, seborrhea), weight loss
5.	Glabellar reflex, blepharospasm, dystonia, striatal deformity, scoliosis, camptocormia	Sleep disorders (REM behaviour disorder, vivid dreams, daytime drowsiness, sleep fragmentation, restless legs syndrome)

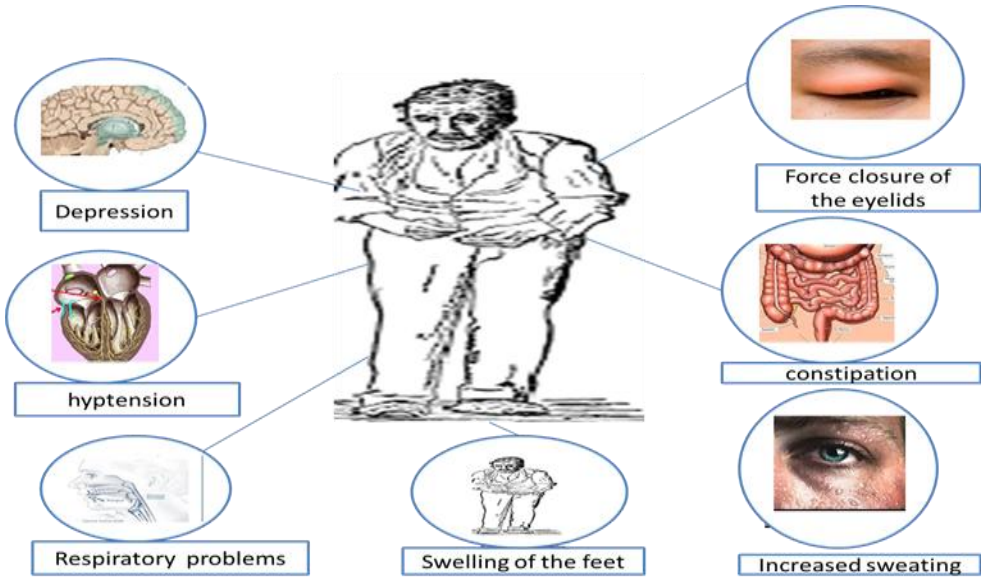

Fig 2: Motor and nonmotor disorders caused by Parkinson's diseases

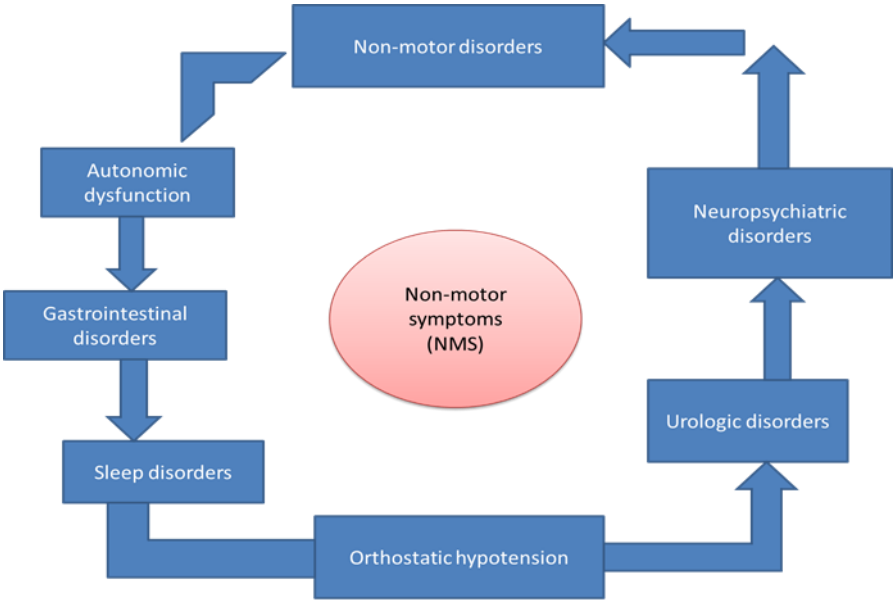

Fig 3: Non-motor symptoms of Parkinson's diseases

PATHWAYS INVOLVED IN PARKINSON'S DISEASE

The major mechanisms known to be involved with Parkinson's disease are dysfunctions in the protein degradation systems: ubiquitin-preoteasome system (UPS) and autophagy, mitochondrial dysfunction, oxidative and nitrative stress and inflammation as described in Fig 4. Mutations in specific genes have been shown to cause Parkinson's disease. These genes code for alpha-synuclein (SNCA), parkin (PRKN), leucine-rich repeat kinase 2 (LRRK2 or dardarin) PTEN-induced putative kinase 1 (PINK1), DJ-1 and ATP13A2. The role of the SNCA gene is important in PD because the alpha-synuclein protein is the main component of Lewy bodies**.**

FGFs (fibroblast growth factors) have potent neurotrophic properties for dopaminergic neurons [21]. They promote DA neuron's development and neurite outgrowth, rescue damaged DA neurons after different toxic insults, and prevent apoptosis. Overexpression of L1CAM (L1 cell adhesion molecule) enhances the survival of imperiled endogenous dopaminergic neurons in the Substantia nigra [22]. RAB3A (member of RAS oncogene family) has been shown to suppress α-syn toxicity in Neuronal models of PD [23]. Fractalkines produced by neurons suppress the activation of microglia and play a neuroprotective role in 6-OHDA-induced (synthetic neurotoxic compound) dopaminergic lesions [24]. Metallothioneins (cysteine-rich, heavy metal binding protein molecules) have been considered as 'defensive proteins' with a role in neuroprotection.

Ubiquitin-proteasome dysfunction

It is a nonlysosomal protein degradation pathway for unwanted intracellular proteins, including misfolded, mutated, mislocated or damaged proteins, and is therefore important in maintaining cell homeostasis (Wang & Maldonado, 2006). It is involved in the regulation of many cellular processes such as cell cycle and division, development and differentiation, apoptosis, cell trafficking and morphogenesis of neuronal networks (Ciechanover, 1998). Dysfunction of the UPS has been shown to be involved in the nigrostriatal neuronal loss.

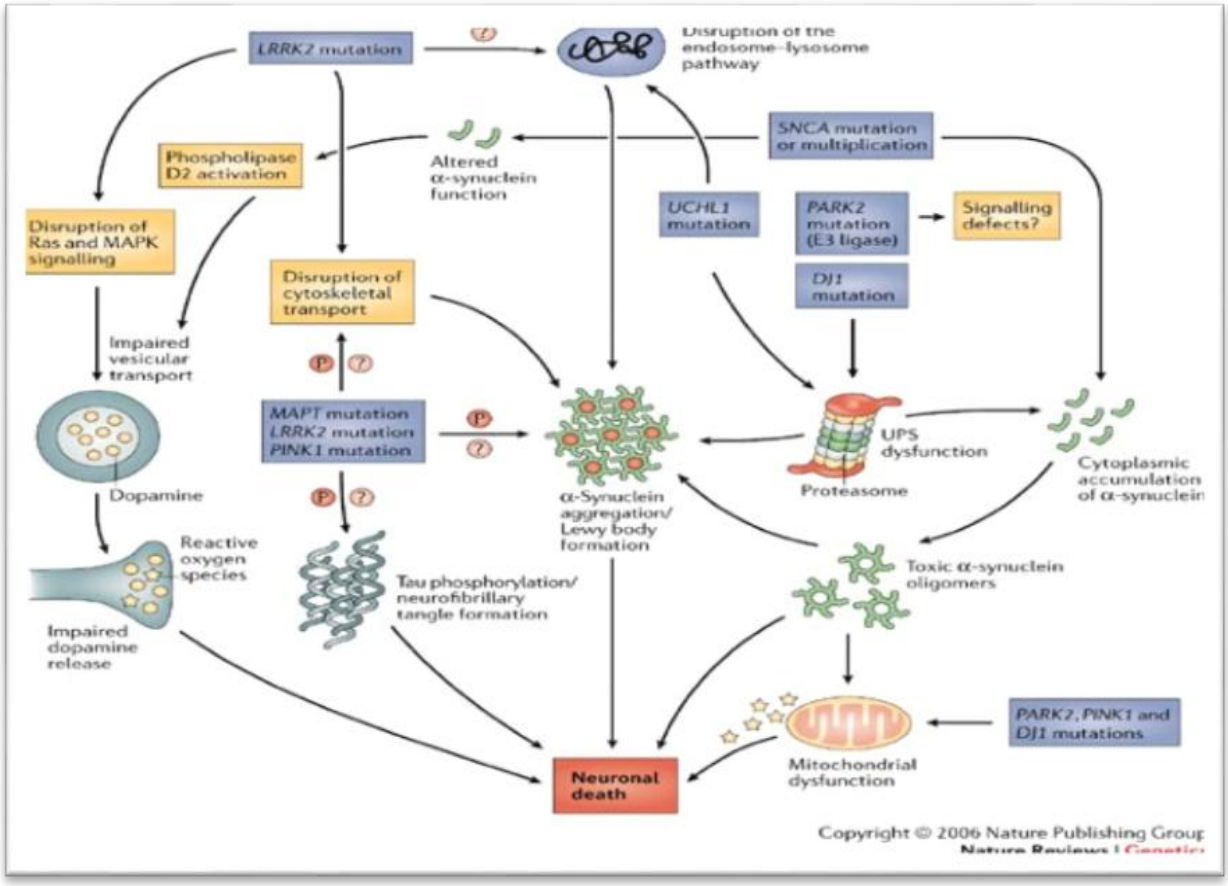

Fig.4: Parkinson's disease pathways map downloaded from Wiki Pathways

Mitochondrial dysfunction

Abnormalities in the mitochondrial respiratory chain have been known to be involved in Parkinson's disease. Impairment in this system results in energy deficiency and oxidative stress that leads cells to be more susceptible to toxins and eventually cell death [25]. The PINK1 gene encodes for the mitochondrial membrane kinase and its mutation is associated with autosomal recessive forms of PD [26].

Oxidative stress

Oxidative stress is defined as the imbalance between reactive oxygen species (ROS) production and antioxidant defense system. It is linked to other components of the degenerative process including, UPS dysfunction and inflammation, but is particularly linked to mitochondrial dysfunction. ROS are produced in the mitochondria as by-products of the electron-transport chain, in the form of superoxide anion (O_2) and hydrogen peroxide (H_2O_2). A defense mechanism consisting of enzymes such as superoxide dismutase (SOD), catalase, glutathione (GSH) and ascorbate convert these radicals into harmless molecules. Oxidative stress occurs when the radicals are generated at increased levels which overwhelm the antioxidant capacity [27].

PREVENTION OF PARKINSON'S DISEASE

Parkinson's disease treatments aim to restore the proper balance of the neurotransmitters acetylcholine and dopamine. This is usually done with medication including yoga and meditation, herbal medication, homeopathy and allopathy including surgery, transplantation and drug theraphy as shown in fig. 5. Generally, this therapy aims to increase levels of dopamine in the brain.

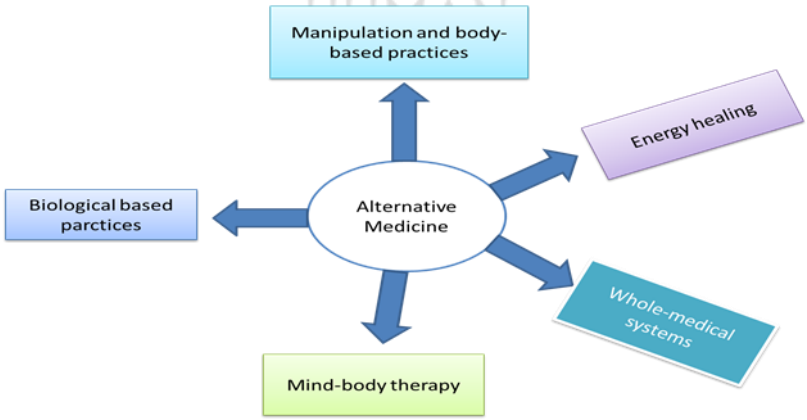

Fig 5: Various ways to prevent Parkinson's Diseases

However, with long-term treatment with L-dopa, more than 50% of patients were found to develop motor response complications approximately after 4 - 5 years of initiation of continuous treatment in 80% of patients treated for 10 years, and in nearly 100% patients with young-onset disease. The complications of long-term treatment with levodopa include-motor fluctuations, dyskinesias, and nonmotor fluctuations are such as mood disturbance,

cognitive dysfunction, dysautonomia and pain. Till date, there are various therapeutic approaches having been developed for the treatment of advanced PD comprising pharmacotherapy, neurotrophic factors, surgical procedures such as DBS, cell-based therapies and gene therapies. The pharmacological and surgical therapies are only aiming to improve the symptoms of PD. All commonly employed PD therapies focus on the amelioration of symptoms and do not cure disease.

At present, as these treatments only alleviate the motor symptoms and remain symptomatic in nature, there is an urgent need for a neuroprotective agent that can prevent further loss of 24 dopaminergic neurones in the substantia nigra pars compacta (SNPc) and eventually halt disease progression. Out of all techniques used in the treatment of Parkinson's diseases, drug therapy is most effective. Drugs that are used for the treatment of Parkinson's disease are as shown in table 2.

Table 2: Drugs used for the treatment of Parkinson's disease.

Drug	**Side effects**
Levodopa	sickness or nausea, sleepiness, vomiting, ostural hypotension, confusion, hallucinations, dyskinesias
Dopamine agonists	nausea and vomiting, headaches, hypotension, confusion, sleepiness, hallucinations, psychosis, dyskinesias, erythromelalgia, pleural fibrosis
Apomorphine	nausea or vomiting, depression, confusion, hallucinations, unusual or inappropriate behavior; slow heart rate, weak pulse, fainting, slow breathing
Glutamate antagonist	fainting, confusion or dizziness, swelling of the ankles or a mottled appearance on the skin of the lower leg
Anticholinergic	dry mouth, blurred vision, urinary retention, confusion, memory impairment; avoid in elderly
COMT inhibitors	potentiates levodopa effects; increased dyskinesia, psychosis, diarrhea
MAO-B-inhibitors	headache, aching joints, indigestion, flu-like symptoms, depression

Surgical Treatment

The role of surgery in treatment of PD has changed dramatically over the past several decades. In the 1940's and 1950's, pallidotomies and thalamotomies were performed to treat

the tremor associated with PD. After the development of L-dopa in the 1960's, neurosurgery was rarely performed to treat PD. Recognition of the limitations of pharmacotherapy and improvement in surgical techniques led to a resurgence of surgery on PD patients in recent years. Surgery is generally reserved for non-demented patients who respond to medical treatment but suffer from intolerable side effects. Decisions regarding which surgical procedure to perform are based on the severity and pattern of each patient's symptoms. 94 Selection of appropriate surgical procedures for appropriate patients is essential to increase the likelihood of benefit. Surgical options include ablative procedures (pallidotomy or thalamotomy), deep brain stimulation (DBS), and tissue transplant. In ablative procedures, an abnormally functioning structure (globes pallidus or thalamus) is disrupted. In DBS, an electrode is placed in the globes pallidus, thalamus, or subthalamic nucleus, to stimulate their function.

CONCLUSION

PD is a brain disorder. It occurs when certain nerve cell (neurons) in a part of the brain called the substantial nigra die or become impaired. These cells produce a vital chemical known as dopamine. Dopamine allows smooth, coordinated function of the body's muscles and movement. When approximately 80% of the dopamine producing cells is damaged, the symptoms of PD appear. In order to develop a suitable clinical treatment, it is important to study and understand the molecular pathways involved in PD are protein degradation systems. Mutations in specific genes have been also studied that are main causing agents of Parkinson's disease. These genes responsible for Parkinson's disease including NADH-UBIQUINONE OXIDOREDUCTASE FLAVOPROTEIN 2; NDUFV2 alphasynuclein (SNCA), parkin (PRKN), leucine-rich repeat kinase 2 (LRRK2 or dardarin), PTEN-induced putative kinase 1 (PINK1), DJ-1 and ATP13A2. There is still no cure for complete eradication of Parkinson disease. Scientists and researchers are still working on developing novel drugs and ways for the treatment of PD. Generally, drugs which are used for cure of Parkinson's disease are anticholinergics, COMT (Catechol-O-methyltransferase) inhibitors, MAO-B inhibitors, glutamate antagonist, apomorphine, dopamine agonists and levodopa. This study is an effort to highlight main features and symptoms of PD, its etiology and pathogenesis, its pathways and ways of prevention so that further in future researchers and scientists can work more on treatment strategies of Parkinson disease.

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