

A Review on Diagnosis and Management of Parkinson's Disease

Saurabh Bhilare¹, Sayali Chavan², Pooja Kadam³, Vivekkumar Redasani⁴

Students^{1,2}, Assistant Professor³, Principal⁴

Department of B. Pharmacy

YSPM'S, Yashoda Technical Campus, Faculty of Pharmacy, Wadhe, Satara

Corresponding Author's Email: skbhilare2019@gmail.com

Abstract

Movement disorders include conditions like Parkinson's disease (PD). It occurs when the brain's nerve cells don't create enough dopamine, a neurotransmitter. Environmental chemical exposure may be a factor. People with the condition may experience difficulty walking, communicating, or performing basic tasks as their symptoms worsen. Since PD cannot be diagnosed with a lab test, diagnosis might be challenging. To diagnose it, medical professionals look at neurological symptoms and medical history. The field of PD management is expanding and aims to develop both novel and enhanced treatment approaches. Physicians can now treat patient-specific issues as they emerge in addition to the primary motor symptoms of Parkinson's disease (PD) thanks to pharmaceutical, surgical, and therapy interventions. This review addresses the current and established options for treating Parkinson's disease (PD) that can offer patient-specific care and lessen adverse effects from standard medicines.

Keywords: *Parkinson's disease, Epidemiology, Diagnosis, Parkinson's treatment*

INTRODUCTION

Parkinson's complaint (PD) is the most common type of primary parkinsonism and the alternate most common progressive neurodegenerative complaint. It affects about 1 of the population over age 50 times and about 2.5 of the population over age 70(1). Its cardinal motor symptoms are earthquake, severity, bradykinesia/akinesia, and postural insecurity, but

the clinical picture includes other motor and non-motor symptoms (NMSs) (2). The diagnosis of PD remains essentially a clinical one, and it is important to recognize the early features together with symptoms and signs suggesting other causes of Parkinsonism (3). In recent years, several causative monogenic mutations have been found. However, these mutations likely account for only a small proportion of all PD cases. The large majority of cases are sporadic in nature. Insights into non-genetic causes are therefore needed to advance the understanding of the pathogenesis of the disease and to develop effective therapeutic interventions (4).

Parkinson's disease (PD) is the second most common neurodegenerative disorder and in the majority of cases, its cause remains unknown. Epidemiology refers to the study of distribution and determinants of health related events and their application in the control of diseases [30]. It affects about 1% of the population over age 50 years and about 2.5% of the population over age 70. The lifetime risk for PD development is 2.0% in men and 1.3% in women (1). Most cases of Parkinson disease are idiopathic, but there are known genetic and environmental contributions. Pesticide, herbicide, and heavy metal exposures are linked to an increased risk of Parkinson disease in some epidemiologic studies, whereas smoking and caffeine use are associated with decreased risks (6).

An estimated 6.1 million individuals globally had a Parkinson disease diagnosis in 2016, 2.4 times higher than in 1990. This increasing prevalence was attributed to improved methods used to detect and diagnose Parkinson disease, greater awareness of the disease, aging populations, longer life expectancy, and possibly increased environmental exposures (eg, pesticides, solvents, metals) associated with industrialization (6). Treatment should be individualized to decrease symptoms while minimizing motor and nonmotor complications. As the disease progresses, treatment can be increasingly complicated, and comanagement with a subspecialist may be required. The most important goal is to help patients maintain maximal autonomy and quality of life (7).

Definition-Parkinson's disease (PD), the second most common neurodegenerative disorder after Alzheimer's disease, was originally described in 1817 by James Parkinson in the classic "Essay on the Shaking Palsy". All the cardinal signs of PD relate to motor dysfunction and include resting tremor, bradykinesia, rigidity and postural reflex impairment. Other

manifestations include psychiatric symptoms such as anxiety and depression and dysautonomic symptoms such as hypotension and constipation, paresthesias, cramps, olfactory dysfunction, and seborrheic dermatitis. As the disease progresses, decreased cognitive ability may appear (8).

Epidemiology

The global burden of Parkinson's complaint (PD) is set to rise in the times to come. In a study on the world's 10 most vibrant nations and Western Europe's 5 most vibrant nations, it was estimated that the number of people with PD will rise from 4.1 to 4.6 million in 2005 by two times to 8.7 to 9.3 million in the time 2030 (4).

Males were 1.5 to two times further affected by PD in a maturity of the studies. Still, this wasn't observed in some studies and others noted a womanish ascendance. The gender difference was less apparent in Asian studies (5).

The crude frequency rate of PD in European countries has been set up to range from 65.6 per 100,000 to 12,500 per 100,000, and the prevalence from 5 per 100,000 to 346 per 100,000. In Asian countries, the crude frequency rates feel to be lower and range from 15 per 100,000 to 328 per 100,000 (9). The prevalence of PD in industrialized countries is generally estimated at 0.3% of the entire population and about 1% in people over 60 years of age (10).

Some challenges in the epidemiological study of Parkinson's disease (11)

No diagnostic test

- Examination by expert most reliable
- No criterion always predicts pathology

Long preclinical period

- Exposure may be years before signs

Late-life disorder

- Risk factor identification retrospective
- Diagnostic accuracy in relatives poor

Relatively rare

- Large base population needed

No registries; not reported

- „True“ distribution of disease not certain

The prevalence of Parkinson's complaint is low before the age of 50 times, but it increases fleetly with age, peaking in utmost studies at around 80 times, presumably because of under opinion with adding age. A spurious drop in Parkinson's complaint prevalence with adding age is likely to do because of the adding frequency of madness, which when present at time of onset of motor symptoms is an rejection criterion for the opinion of Parkinson's complaint(12).

A recent systemic review of the prevalence and incidence of PD in Asia concluded that the prevalence and incidence of PD in Asia countries was slightly lower than in Western countries. Six of the most popular countries are in Asia (China, India, Indonesia, Pakistan, Bangladesh, and Japan) and the number of PD patients in these counties is expected to increase from 2.57 million in 2005 to 6.17 million in 2030 (4).

Etiology

The view of etiological factors in PD has changed remarkably from one of a purely sporadic basis to the view that both environmental and genetic factors contribute to the onset of the illness to a point now where increasingly genetic predisposition must be seen as a major contributor to the underlying cause (13).

Environmental factor

The specific etiology of Parkinson's complaint (PD) isn't known. Epidemiologic studies indicate that a number of factors may increase the threat of developing PD. These include exposure to well water, fungicides, dressings, artificial chemicals, wood pulp manufactories, husbandry, and living in a pastoral terrain (14).

Epidemiological studies lead one to suspect the part of the terrain, as indicated by

- a more elevated frequency with pastoral living

- well- water consumption
- a more elevated frequency in industrialized countries; and
- pesticide and fungicide exposure.

The actuality of both inheritable and environmental susceptibility, the origin of PD seems to be multifactorial. The further patent demonstration is the part of smoking. Epidemiological studies establish an inverse relation between the frequency of PD and smoking (15).

Genetic Factor

There has been considerable interest in the potential role of genetic factors in the etiology of PD. Approximately 5–10% of PD patients have a familial form of parkinsonism with an autosomal-dominant pattern of inheritance(14).

The younger the child at the time the parent developed PD, the higher the risk for the child. This relationship was especially apparent when the affected parent was the mother. The degree to which parents and children share their environment usually decreases with age. Furthermore, for inherited illnesses, the risk for the child is usually related to parental age at onset (10).

The VA binary study revealed no difference in concordance between monozygotic and dizygotic halves of PD cases progressed 60 times or aged but a significantly increased prevalence was observed in monozygotic halves who developed PD at lower than 50 times of age. This suggests that inheritable factors are important in youthful- onset cases but aren't likely to play a major part in cases with sporadic PD. A number of seeker genes have been screened and set up not to be associated with an increased threat of PD (14).

PATHOPHYSIOLOGY

The main pathological features of PD are the loss of dopaminergic neurons with subsequent depigmentation of the SN pc and the presence of LBs (2). The pathological hallmark of Parkinson's disease and MPTP-induced Parkinsonism is the degeneration of dopaminergic cells within the substantia nigra and the subsequent dopamine depletion of the striatum(16).

Although neither the loss of dopaminergic neurons in the substantia nigra nor the deposit of α -synuclein in neurons is specific for PD, these two major neuro-pathologies are specific for a definitive opinion of idiopathic PD when applied together (17).

These complaint mechanisms inclusively affect in accelerated neuronal death of primarily dopaminergic neurons, but the neuropathology involves multiple other motor and non-motor circuits. Loss of nigrostriatal dopamine cells causes a grade of striatal dopamine reduction producing an imbalance between direct (facilitatory) and circular (inhibitory) pathways through the rudimentary ganglia, performing in bradykinesia. Neurophysiological recordings conceptualized bradykinesia as an imbalance between different oscillatory measures too important (anti-kinetic) beta exertion and too little (prokinetic) gamma exertion (18).

Therefore mortal PD earthquake is depending on the nigrostriatal deficiency but once this is present, the earthquake doesn't depend on the inflexibility of this deficiency. also, in the MPTP primates, there's no correlation between midbrain dopamine pathology and earthquake. thus, it's possible that, transmitter systems other than dopamine (e.g., cholinergic, serotonergic) or neural circuits other than the rudimentary ganglia do play a critical cumulative part for this symptom (16).

Parkinson's disease is linked in a non-unique way to a massive and selective loss of sub-populations of mesencephalic dopaminergic cells. Non-dopaminergic neurons are also altered, and not all dopaminergic neurons are affected (15).

Non-dopaminergic lesions – (15)

Non-dopaminergic neurotransmitters affected in PD are a) noradrenaline (NA); b) serotonin (5-HT); c) glutamic acid (GLU); d) gamma-aminobutyric acid (GABA); e) neuropeptides; and, f) acetylcholine (ACh). Non-DA responsive signs are axial signs (dysarthria, gait diseases, postural insecurity), dysautonomia (constipation, urinary diseases, orthostatic hypotension), and cognitive impairment.

Noradrenaline

Locus coeruleus, which contains NA neurons, is altered in PD (19). Therapeutics which restore noradrenergic transmission should be effective for the treatment of gait disorders, depression and dementia, but this is not confirmed at present.

Serotonine

Dropped attention of 5-HT in the smarts of parkinsonian cases may explain depression (20). On the contrary, relative hyperactivity of 5-HT may induce somnolence and hallucinations in PD (21).

Glutamic acid

Glutamic acid is an excitotoxic amino acid that may play a pattern in neurotoxicity. Glutamatergic receptors are unchanged in PD, and GLU antagonists may have an implicit remedial effect on akinesia and severity, and may also potentiate the effectiveness of L-dopa (22). However, no effective NMDA antagonist has been used to date.

GABA

The striatal gabaergic afferent neurons are the target of nigrostriatal dopaminergic neurons. Degeneration of these dopaminergic neurons results in an increase in the exertion of this gabaergic afferent (23).

Acetylcholine

The alteration of basal forebrain cholinergic neurons, particularly in the nucleus basalis of Meynert, have been reported in PD. This cholinergic denervation participates in cognitive deficits (24). Striatal cholinergic interneurons are unchanged in PD. Muscarinic receptor blockers are classically used in the treatment of the motor signs of PD, but should be used only in non-demented patients (25).

Heterogeneity in dopaminergic lesions

The mesencephalic region contains five neuronal groups of dopaminergic neurons: a) the SN, which projects to the striatum; b) medial and medio-ventral regions, which project the frontal cortex and limbic system; c) the peri and retro-rubral region, named area A8; d) the SN lateral part; and, e) the peri-aqueductal region. In PD, neuronal loss is large in SN compacta (80%),

discrete in the peri-aqueducal region (5%), and intermediate in the other groups of dopaminergic cells (26). This distribution is not seen in normal aging and in other parkinsonian syndromes. The more vulnerable neurons produce more oxygen free radicals than those which are less altered.

Oxidative stress

Oxidative stress and differences in protein running may be involved in the medium of whims cell death. Free revolutionaries produced by cellular metabolism are potentially poisonous for the cell. They're typically controlled by defensive mechanisms, similar as superoxide dismutase, catalase, and glutathioneperoxidase. Oxidative stress is grounded on an excess of free revolutionariesand shy defense mechanisms. Dopaminergic neurons produce a lot of free revolutionaries, in part linked to DA catabolism by oxidative declination (mono- amine oxidase induce hydrogen peroxide) (27), and auto-oxidative mecha-nisms (synthesis of nouromelanin and free radicals) (28). On the other hand, SN contains high concentra-tions of iron, which participates in free radical production (29).

Apoptosis

In PD neuronal death consists of apoptosis or programmed cell death, with the characteristic aspects of cellular retraction, chromatin condensation, nuclear fragmentation, without the alteration of cytoplasmic organelles (30). However, a recent study using highly selective methods for the detection of DNA fragmentation did not find evidence of neuronal apoptosis in long- standing PD (31). Oxygen free revolutionaries may also be involved in apoptosis. Oxidative stress is a potent detector and middleman of apoptosis touched off by other stimulants[37]. Apoptosis can be activated by tumor necrosis factor alpha (TNF alpha) (32), which have been detected in microglial cells in the SN of patients with Parkinson's disease (33).

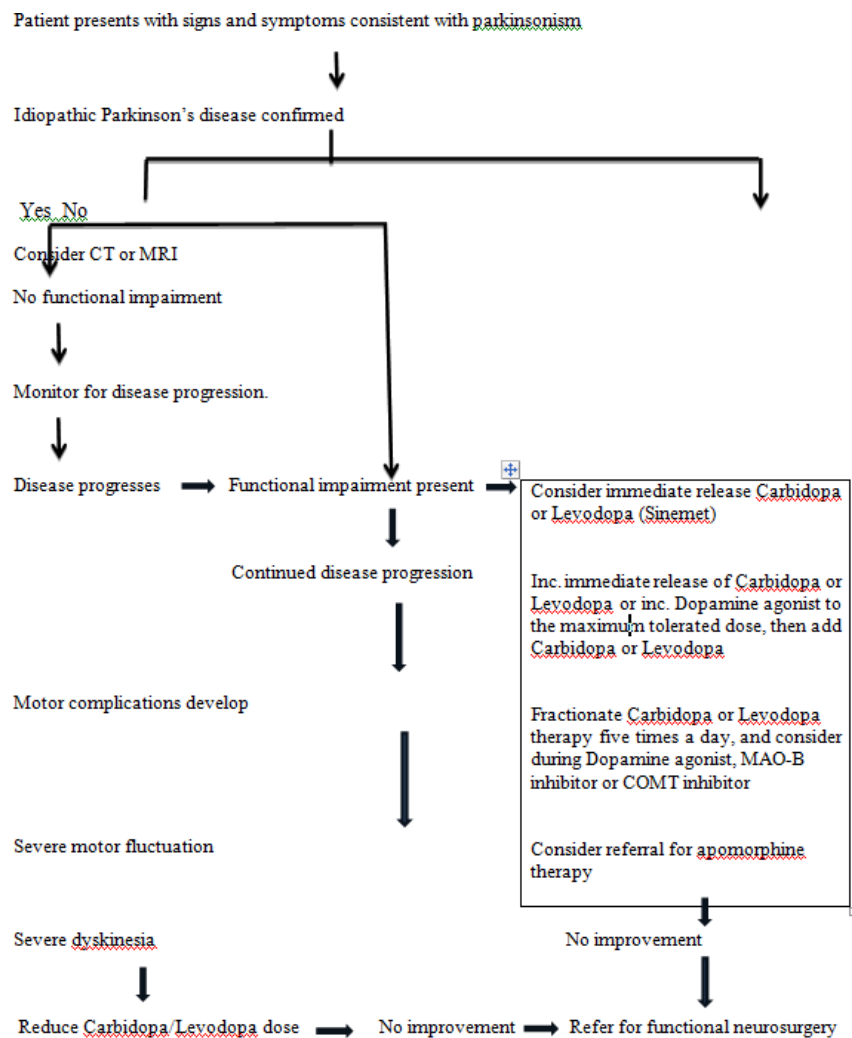
Symptoms

- Motor Symptoms – (34)
 - Resting tremor
 - Bradykinesia
 - Rigidity
 - Shufflind gait

-
- Postural instability
 - Decreased eye blink rate
 - Blurred vision
 - masked facial expression (hypomimia),
 - impaired upward gaze
 - dystonia
 - stooped posture
 - difficulty turning in bed
 - kyphosis
 - scoliosis,
 - shuffling gait,
 - freezing (inability to move) and speech impairment,
 - hypophonia (increasingly soft voice)
 - palilalia (repetition of word or phrase)
 - Non – motor Symptoms – (35)
 - ✓ Neuropsychiatric symptoms
 - Depression and depressive symptoms
 - Anxiety and anxiety symptoms
 - Apathy
 - Impulse control and related disorders
 - Dementia
 - Cognitive impairment (other than dementia; mainly mild cognitive impairment)
 - ✓ Autonomic dysfunction
 - Drooling
 - Urinary dysfunction
 - Erectile dysfunction
 - Gastrointestinal dysfunction
 - Excessive sweating
 - ✓ Disorders of sleep and wakefulness

- Sleep fragmentation and insomnia
 - Rapid eye movement sleep behavior disorder
 - Excessive daytime sleepiness
- ✓ Others
- Pain
 - Fatigue
 - Ophthalmologic dysfunction

Diagnosis and Management – (7)



Treatment – (7)

FDA – Approved Medication for Parkinson`s Disease

Medication	Adverse effects	Indications and comments
Anticholinergics Benztropine (Cogentin), trihexyphenidyl (Artane)	Dry mouth, dry eyes, constipation, hypotension, cognitive impairment, urinary retention	Useful for symptomatic control of Parkinson`s disease (benefits are mild to moderate); associated with more adverse effects than other drugs
Carbidopa/levodopa Immediate- and sustained- release carbidopa/ levodopa (Sinemet)	Nausea, somnolence, dyskinesia, hypotension, hallucinations	Levodopa is the most effective medication and remains the primary treatment for symptomatic Parkinson`s disease; no added benefit for motor complications with sustained- release versus immediate- release preparations
COMT inhibitors Entacapone (Comtan) Tolcapone (Tasmar)	Diarrhea; exacerbates levodopa adverse effects; bright orange urine Diarrhea; exacerbates levodopa adverse effects; rare liver failure (liver function monitoring needed)	Useful for managing motor fluctuations (“wearing-off” effect) in patients taking levodopa; levodopa dose may need to be reduced if dyskinesia appears
Dopamine agonists Bromocriptine (Parlodel)	Nausea, headache, dizziness	Useful for early and advanced

Pergolide (Permax)	Useful for early and advanced disease Somnolence; hallucinations; nausea; edema; fibrosis of cardiac valves, lung, and retroperitoneum; retroperitoneal and pulmonary fibrosis	disease Useful for the initial treatment of parkinsonism and as adjunct therapy in patients taking levodopa
Pramipexole (Mirapex), Ropinirole (Requip)	Nausea, sleep attacks, edema, hallucinations, hypotension	Useful for early disease and in patients with Parkinson's disease and motor fluctuations
MAO-B inhibitors Selegiline (Eldepryl) Rasagiline (Azilect)	Nausea, insomnia, drug interactions with other MAO inhibitors/tyramine Weight loss, hypotension, dry mouth, drug interactions with other MAO inhibitors/tyramine	Useful for symptomatic control of Parkinson's disease (benefits are mild to moderate) and as adjuvant therapy for patients with Parkinson's disease and motor fluctuations
NMDA receptor inhibitor Amantadine (Symmetrel)	Nausea, hypotension, hallucinations, confusion, edema	Useful for treating akinesia, rigidity, tremor, dyskinesia

Treatment of Non-motor symptoms - (36)

Symptoms	Treatment
Depression	Norepinephrine antidepressants such as: Amitriptyline, imipramine, nortriptyline, and desipramine SSRI's such as fluoxetine and nefazodone Second generation non-ergot agonists, for example, Pramipexole and ropinirole Psychotherapy
Anxiety	Buspirone and SSRI Cognitive Behavioral Therapy
Apathy	Piribedil Dopamine enhancing medication, for example, Pramipexole and ropinirole
Dementia	Rivastigmine
Front Executive Dysfunction	Cholinesterase inhibitors
EDS	Correct timing of medication CNS stimulants: Modafinil, Ritalin Avoid benzodiazepine
MCI	Cholinesterase inhibitors
RBD	Clonazepam Donepezil Melatonin Pramipexole
Incontinence	Anticholinergic drugs α -Blockers Pelvic floor muscle therapy Lifestyle changes
Hyperhidrosis	Dopamine agonist therapy Apomorphine
Drooling	Anti-Parkinson's drug therapy

	Speech and language therapy Chewing gum Trihexyphenidyl Amitriptyline
Sexual dysfunction	ED: Phosphodiesterase inhibitors, for example, Sildenafil Hypersexuality: Pergolide mesylate with L-DOPA Counseling
Postural hypotension	Fludrocortisone
Non-motor symptoms fluctuation	COMT inhibitors . IMAOB . Apomorphine infusion . Subthalamic deep brain stimulation . Amatine . Free salt intake . Increased fluid intake
Pain	Musculoskeletal pain: NSAIDS, physical therapy and exercise program Dystonic pain: deep brain stimulation, trihexyphenidyl Pain from akathisia: managed with dopaminergic treatments Central pain: analgesics, opiates, and atypical neuroleptics
Speech dysfunction	Behavioral speech therapy LSVT LOUD
Constipation	Diet of high fiber foods and fluids Exercise Reduction of anticholinergic medication Macrogol Milk of magnesia Psyllium Polyethylene glycol Laxatives and enemas as a last resort
Dysphagia	Softening solid food and thickening liquids before

	consumption Gastrostomy
Ocular dysfunction	Artificial tears Bifocal and progressive lenses
RLS	Pramipexole, ropinirole Pregabalin Simplify psychoactive medications with atypical neuroleptics, for example, clozapine Gabapentin enacarbil to treat PLMS Oxycodone with naloxone

CONCLUSION

Parkinson's is a neurological complaint that's substantially characterized by problems with body movements, although other symptoms can also do. Presently there's no given cause of understanding of why a person develops Parkinson's. There are numerous propositions as to the causes and it's generally allowed that multiple factors are responsible. No, there's presently no cure for Parkinson's complaint. Still, there are drugs that can help to treat the symptoms of the complaint. Research is ongoing to find new treatments for Parkinson's complaint. Gene remedy, which involves delivering normal genes directly to your brain to help the death of brain cells, is one illustration. Other exploration is looking at whether whims cells that are lost in people with Parkinson's complaint can be replaced with new healthy cells from stem cells grown in the laboratory.

Parkinson's disease represents a major clinical challenge since it's one of the most common neurodegenerative conditions, affects primarily a population of aging individualities, a group that's growing fleetly in the world, and lacks a remedial means to impact the inexorable loss of dopaminergic innervation. Parkinson's Disease itself doesn't beget death but is associated with increased morbidity and mortality. Knowledge of the complaint instantiations, treatments, and progressive long- term course is essential for optimal care and enhanced quality of life for people with Parkinson's complaint.

REFERENCES

1. Marvanova M. Introduction to Parkinson disease (PD) and its complications. *Ment Health Clin* [Internet]. 2016; 6(5):229-35.
2. R. BALESTRINO AND A. H. V. SCHAPIRA, Parkinson`s Disease, *European Journal of Neurology* 2020, 27: 27–42.
3. C. A. Davie, A review of Parkinson`s disease, *British Medical Bulletin* 2008; 86: 109–127.
4. Louis CS Tan, Epidemiology of Parkinson`s disease, *Neurology Asia* 2013; 18(3): 231 – 238.
5. M.M. ABBAS ET AL. Epidemiology of Parkinson`s Disease-East Versus West, *MOVEMENT DISORDERS CLINICAL PRACTICE* 2018; 5(1): 14–28.
6. Melissa J. Armstrong, Diagnosis and Treatment of Parkinson Disease, *JAMA*. 2020; 323(6):548-560.
7. SHOBHA S. RAO ET AL, Parkinson`s Disease: Diagnosis and Treatment, *American Family Physician* December 15, 2006 , Volume 74, Number 12.
8. Karin Wirdefeldt, Hans-Olov Adami, Philip Cole, Dimitrios Trichopoulos, Jack Mandel. Epidemiology and etiology of Parkinson`s disease: a review of the evidence. *European Journal of Epidemiology*, 2011, 26 (S1), pp.1-58.
9. Shin-Yuan Chen, the Epidemiology of Parkinson`s disease, *TZU CHI MED J* June 2010 Vol 22 No 2.
10. Lonneke M L de Lau, Monique M B Breteler, Epidemiology of Parkinson`s disease, *Lancet Neurol* 2006; 5: 525–35.
11. M. KASTEN ET AL. Epidemiology of Parkinson`s disease, *Handbook of Clinical Neurology*, Vol. 83 (3rd series), Page no. 129-151.
12. Alberto Ascherio, Michael A Schwarzschild, The epidemiology of Parkinson`s disease: risk factors and prevention, *Lancet Nrurol* 2016; 15: 1257-72.
13. SCHAPIRA AND JENNER, Etiology and Pathogenesis of Parkinson`s Disease, *Movement Disorder*, Vol 26, no. 6, 2011.
14. OLANOW and TATTON ETIOLOGY AND PATHOGENESIS OF PARKINSON`S DISEASE, *Annual Review of Neuroscience* Volume 22, 1999, Pg. no. 123-144.
15. A.M. Bonnet, J.L. Houeto, Pathophysiology of Parkinson's disease, *Biomed & Pharmacotherapy* 1999 ; 53 : 117-21.

16. H. BERGMAN AND G. DEUSCHL, Pathophysiology of Parkinson's Disease: From Clinical Neurology to Basic Neuroscience and Back, Movement Disorder Vol. 17, Suppl. 3, 2002, pp. S28–S40.
17. Werner Poewe et al. PARKINSON DISEASE, Nature Reviews Disease Primers, Pg no. 1-52.
18. Bastiaan R Bloem, Et al, Parkinson's disease, Lancet 2021; 397: 2284–303.
19. German DC, Manaye KK, White CL, Woodward DJ, McIntire DD, Smith WK, et al. Disease-specific patterns of locus coeruleus cell loss. Ann Neurol 1992; 32: 667-76.
20. Van Praag HM, De Haan S. Central serotonin metabolism and frequency of depression. Psychiatr Res 1979;1: 219-24.
21. Melamed E, Zoldan J, Friedberg G, Goldberg-Stem H. Hallucinosi in Parkinson's disease due to central serotonergic hyperactivity? Mov Disord 1993;8: 406.
22. Greenamyre JT, O'Brien CF. N-methyl-D-aspartate antagonists in the treatment of Parkinson's disease. Arch Neur 1991;48: 977-81.
23. Kish S J, Shannak K, Hornykiewicz O. Uneven pattern of dopamine loss in the striatum of patients with Parkinson's disease. N Engl J Med 1988;318: 876-80.
24. Whitehouse JP, Hedreen JC, White CL, Price D. Basal forebrain neurons in the dementia of Parkinson's disease. Ann Neurol 1983;13: 243-8.
25. Barbeau A. The pathogenesis of Parkinson's disease: a new hypothesis. Can Med Assoc J 1962;87: 802-7.
26. Hirsch EC, Graybiel AM, Agid Y. Melanized dopaminergic neurons are differentially susceptible to degeneration in Parkinson's disease. Nature 1988;334: 345-8.
27. Spina MB, Cohen G. Dopamine turnover and glutathione oxidation: implications for Parkinson's disease. Proc Natl Acad Sci USA 1989;86: 1398-400.
28. Graham DG, Tiffany SM, Bell WR. Auto-oxidation versus covalent binding of quinones as the mechanism of toxicity of dopamine, 6-hydroxydopamine and related compounds towards C-1300 neuroblastoma cells, in vitro. Mol Pharmacol 1978;14: 644-53.
29. Jellinger K, Paulus W, Grundke-Iqbal I, Riederer P, Youdim MBH. Brain iron and ferritin in Parkinson's disease and Alzheimer's disease. J Neural transm 1990;2: 327-40.

30. Anglade P, Vyas S, Javoy-Agid F, Herrero MT, Michel PP, Marquez J, et al. Apoptosis and autophagy in nigral neurons of patients with PD. *Histo Histopathol*. In press 1997.
31. Bareti RB, Daniel SE, Blunt SB. Glial pathology but absence of apoptotic nigral neurons in long-standing Parkinson's disease. *Mov Disord* 1998;2; 221-7.
32. Kolesnick R, Golbe DU. The sphingomyelin pathway in tumor necrosis factor and interleukin-1 signaling. *Cell* 1994;77: 325-8.
33. Boka G, Anglade P, Wallach D, Javoy-Agid F, Agid Y, Hirsch EC. Immunocytochemical analysis of tumor necrosis factor and its receptors in Parkinson's disease. *Neurosci Lett* 1994; 172: 151-4.
34. Janice M. Beitz, Parkinson's disease: a review, [Frontiers in Bioscience S6, 65-74, January 1, 2014].
35. SEPI ET AL, Update on Treatments for Nonmotor Symptoms of Parkinson's Disease-An Evidence-Based Medicine Review, *Movement Disorders*, Vol. 34, No. 2, 2019.
36. Rana A. Q. Et al, Parkinson's disease: a review of non-motor symptoms, *Expert Rev. Neurother.* 15(5), 549–562 (2015).
37. Ziv I, Melamed E, Nardi N, Luria D, Achiron A, Offen D, et al. Dopamine induces apoptosis-like cell death in cultured chick sympathetic neurons - a possible novel pathogenetic mechanism in Parkinson's disease. *Neurosci Lett* 1994; 170: 136-40.