Recent Trends on Parkinson's Diseases Therapy

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ABSTRACT

Parkinson's disease is a chronic movement problem found in neurology, but it's difficult to diagnose and treat. Because PD patients have a wide range of motor and non-motor symptoms, the diagnosis is clinical and can be challenging. The medical care of Parkinson's disease patients is tough due to a lack of pharmacological options and the use of levodopa as the backbone of treatment. However, in Parkinson's disease patients using levodopa, levodopa induced dyskinesia (LID) is prevalent. This is a common adverse effect that occurs after a lengthy period of treatment, but it can also occur after a few days or months of medication. Different surgical techniques, such as unilateral pallidotomy and deep brain stimulation, have had excellent outcomes in PD patients who are unable to control their symptoms with drugs alone.

Keywords: Parkinson's diseases, Pharmacological management, surgical treatment.

INTRODUCTION

Parkinson's disease (PD) was essentially defined as a "shaking palsy" by Dr. James Parkinson in 1817. It's a long-term, progressive neurodegenerative illness with both motor and nonmotor symptoms. Through its gradual degenerative effects on movement and muscular function, the illness has a substantial clinical impact on patients, families, and careers. Although the existence of nonmotor symptoms suggests neuronal loss in nondopaminergic regions, the loss of striatal dopaminergic neurons is ascribed to the motor symptoms of PD. The word Parkinsonism refers to a symptom complex that includes resting tremor, bradykinesia, and muscular stiffness, and is used to define the motor characteristics of Parkinson's disease. Although Parkinson's disease is the most prevalent cause of Parkinsonism, there are a variety of secondary causes, such as disorders that resemble PD and drug-induced causes.[1]

According to research, pathophysiological changes linked with PD may begin before motor symptoms appear, and may manifest themselves in a variety of nonmotor manifestations such as sleep difficulties, depression, and cognitive abnormalities. The enthusiasm for research that focuses on protective or preventive medicines has been fueled by evidence from this preclinical period.

One of the most frequent neurodegenerative diseases is Parkinson's disease. According to the Parkinson's Disorder Foundation, the disease affects around 1 million people in the United States. 5 In the United States, there are about 20 instances of Parkinson's disease per 100,000 persons per year (60,000 per year), with a typical onset age of around 60 years. In persons 60 years and older, the prevalence of Parkinson's disease is estimated to be around 1%, increasing to 1% to 3% in those aged 80 and up. However, it is crucial to note that these figures do not include instances that have yet to be diagnosed.[2]

PD has been diagnosed in people in their 30s and 40s, despite the fact that it is usually a disease of the elderly. Gender variations in PD incidence are represented in a 3:2 ratio of males to females, with females experiencing a delayed start due to estrogen's neuroprotective effects on the nigrostriatal dopaminergic pathway.

The unpredictable but noticeable course of Parkinson's disease has a substantial impact on individuals, families, and society. Advanced and end-stage illness can result in major consequences, such as pneumonia, which is typically fatal. The current therapy focuses on symptomatic relief. Patients with Parkinson's disease may benefit from a multidisciplinary approach to therapy that involves movement experts, social workers, pharmacists, and other health care providers, according to research.

PD is linked to a number of risk factors and genetic abnormalities. Oxidative stress, the generation of free radicals, and a variety of environmental toxins are all risk factors for the illness. Limited evidence supports genetic links to Parkinson's disease, with several gene abnormalities being found. Intriguingly, there is an inverse link between cigarette smoking, caffeine use, and the chance of acquiring Parkinson's disease. The beneficial effects of tobacco smoking may be due to inhibition of the

enzyme monoamine oxidase (MAO), whereas the advantages of caffeine may be due to its adenosine antagonist action. The fact that the frequency of Parkinson's disease varies across the world shows that environmental, genetic, and ethnic variables may all play a role in disease development. Biomedical research on people with Parkinson's disease is still going on, and it might assist to uncover new risk factors and guide future preventative and treatment decisions.

Environmental Contributors

Several environmental contaminants have been linked to the start of Parkinson's disease, however the evidence is mixed. According to certain research, occupational chemical exposure may be connected to the development of Parkinson's disease. Agriculture, as well as dealing with pesticides and heavy metals, are among the jobs that have been researched. Electrical occupations, dealing with extremely low frequency-magnetic fields, diesel motor fumes, and solvents have all been investigated as having no effect. Rural living as a cause of idiopathic PD has long been a contentious subject in PD research. Some studies have shown no relation between rural living and PD, while others have suggested that urban life may increase the incidence of PD. Significant associations between industrial airborne heavy metal pollution and ambient air pollution from traffic and an increased risk of PD development have also been discovered in studies done in densely populated metropolitan regions. Other research have shown no link between geographic location and the rise in the incidence of Parkinson's disease. Other studies, however, have linked rural exposure to an increased risk. The fact that rural areas have a proportionately larger number of elderly people may explain why there are more cases of Parkinson's disease there.[3]

Epidemiology

Epidemiology The incidence and frequency of Parkinson's disease rises with age, with 1% of those over 65 years old having the disease. The beginning of parkinsonian symptoms before the age of 40 is known as early-onset Parkinson's disease (EOPD). It accounts for 3% to 5% of all Parkinson's disease cases. It is divided into two types: 'juvenile' (occurring before the age of 21) and 'young-onset' (occurring after the age of 21). (YOPD, occurring in the age range of 21- 40 years). In most societies, males are twice as likely as women to get Parkinson's disease. Female sex hormones appear to have a protective impact. This male preponderance might be explained by gender-related genetic processes or gender-specific variations in exposure to environmental risk factors. There is no comprehensive and extensive epidemiological data on Parkinson's disease in India. In a population of 63,645 people in rural Kashmir in northern India, Razdan et al. found a crude prevalence rate of 14.1 per 100,000. Over the age of 60, the prevalence rate was 247/100,000. Bangalore, in the southern portion of India, had a low prevalence rate of 27/100,000, whereas rural Bengal, in the eastern part of India, had a rate of 16.1/100,000. In a

community of 14,010 Parsis residing in colonies in Mumbai, Western India, Bharucha et al. found a high crude prevalence rate of 328.3/100,000.[4]

Pathophysiology

Parkinson's disease genetics Only 5–10% of all instances of Parkinson's disease are genetic. A patient's family history, early start of disease, and certain clinical symptoms (e.g., dystonia as a presenting symptom) raise suspicion of the genetic type of the disease. More than 10% of YOPD patients have a genetic foundation, and the number of genetically characterised cases jumps to more than 40% if the disease begins before the age of 30. The primary genes discovered and proved to be causative in PD are Parkin (PARK2), Alpha synuclein (SNCA-PARK1/PARK4), Leucine rich repeat kinase2 (LRRK2/PARK8), PTEN induced putative kinase 1 (PINK1/PARK6), DJ1 (PARK7), ubiquitin C-terminal hydrolase like 1 (UCH-L1), and ATPase type 13A2 (ATP13A2).[5]

In India, the genetics of Parkinson's disease In Indian case series, mutations in the Parkinson's gene are the most common, ranging from 1.96 percent to 39.1 percent. SNCA has no mutations, while DJ1, PINK1, and LRRK2 have fewer. Parkin gene mutations have been linked to autosomal recessive (AR) early onset PD and have been shown to differ significantly amongst people from different parts of India. In 2006, Chaudhary et al. found that Parkinson's mutations were responsible for 14.3 percent of familial PD, 6.9% of young onset (age of onset 40 years), and 5.9% of late onset (age of onset 41 years) random PD. In a research from the southern region of India, Padma MV et al. found Parkinson's mutations in 68 percent of early-onset PD patients. It is impossible to distinguish Parkinson's positive early onset PD patients from Parkinson's negative individuals based on clinical characteristics alone. DJ-1 mutations (found in AR Parkinsonism) cause PD symptoms to appear early and progress slowly. These mutations are characterised by a favorable response to levodopa and are frequently linked to dystonia. In the Indian population, the prevalence of DJ1 mutations (AR) in individuals with PD is low (5%). Two more Indian researches investigated the incidence of DJ1 mutations in Parkinson's disease patients. According to one research, DJ1 variations are found in 3.9 %, whereas another study found no harmful alterations.[6]

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Parkinson's negative individuals based on clinical characteristics alone.[7-8] DJ-1 mutations (found in AR Parkinsonism) cause PD symptoms to appear early and progress slowly. These mutations are characterised by a favourable response to levodopa and are frequently linked to dystonia. In the Indian population, the prevalence of DJ1 mutations (AR) in individuals with PD is low (5%). Two more Indian research investigated the incidence of DJ1 mutations in Parkinson's disease patients. One research found that 3.9 % of DJ1 variations are harmful, whereas another study found no pathogenic mutations.

PD is a condition of the extrapyramidal system, which includes motor structures of the basal ganglia. It is defined by a decrease of dopaminergic activity and therefore impaired motor function, which leads to clinical symptoms. Although the appearance of nonmotor features tends to suggest that other neurotransmitters from the glutamatergic, serotonergic, cholinergic, and adrenergic systems, as well as the neuromodulators adenosine and enkephalins, are involved, research in the late 1950s outlined striatal dopamine depletion as the primary cause of clinical manifestations in Parkinson's disease. Further data shows that PD may develop in the anterior olfactory nucleus and the dorsal motor nucleus of the vagal and glossopharyngeal nerves, indicating a disease pattern that starts in the brain stem and progresses to higher cortical levels. The loss of pigmented dopaminergic neurons and the appearance of Lewy bodies are histological characteristics of Parkinson's disease (LBs).[9]

Individuals with Parkinson's disease lose dopaminergic capability as dopaminergic neurons in the substantia nigra pars compacta (SNpc) that connect to the striatum degrade (the nigrostriatal pathway). Patients often suffer motor symptoms of Parkinson's disease only after 50 % to 80 % of dopaminergic neurons have died, indicating the presence of a compensatory mechanism in the early stages of the disease. D1 (excitatory type) and D2 (inhibitory type) dopamine receptors impact motor activity in the extrapyramidal system. The basal ganglia, which includes the internal globus pallidal segment (GPi) of the ventral striatum, and the pars reticulata section of the substantia nigra, are components of this system (SNpr). These parts are connected to bigger circuits in the thalamus and cortex. The loss of dopamine in the striatum of Parkinson's patients causes an increase in activity in the GPi/SNpr circuits, which leads to GABA malfunction and thalamus inhibition. As a result of the thalamus's reduced capacity to engage the frontal cortex, motor activity in people with Parkinson's disease is reduced. As a result, dopaminergic treatments that restore dopamine activity in the striatum by activating D2 and D1 receptors promote clinical improvement in PD motor symptoms. Furthermore, due to the lack of dopamine's usual inhibitory function, dopaminergic depletion causes not only reduced thalamic activation but also increased cholinergic activity. The evidence that PD is caused by a diffuse global network malfunction at numerous levels in the neurological system continues to grow.

The presence of LBs, which are intracellular cytoplasmic aggregates made of proteins, lipids, and other components, is another prominent histological characteristic of PD. LBs have also been recognised as important markers of chronic neurodegenerative disorders, including as Parkinson's disease. Round structures with radiating fibrils have been identified in dopaminergic neurons in the substantia nigra of Parkinson's disease patients. According to study, they may develop as a result of recalcitrant proteolytic processes involving aberrant disintegration or overproduction induced by genetic anomalies. Alpha-synuclein (Syn) protein gene mutations have been discovered to aggregate and produce insoluble fibrils linked with LBs; Syn proteins have been identified as a possible target for future PD treatment.[10]

Excessive synthesis of misfolded versions of ubiquitin proteins, which are important in protein recycling, leads to the creation of LBs. The ubiquitin proteasome system is malfunctioning, which leads to the accumulation of these proteins (UPS). The creation of LBs appears to have a part in the neurodegeneration that is so common in Parkinson's disease, with distinct lesion patterns reported at different stages of the disease. Lesion patterns in the medulla, dorsal nucleus, and pons may promote early (premotor) olfactory and rapid eye movement (REM) elements of Parkinson Disease. Lesions in the nigrostriatal region cause the prevalent neurological symptoms of Parkinson's disease in the chronic phase. LBs are also linked to PD dementia, just as they are in people with dementia caused by LBs (DLB). The clinical presentations of PD and DLB differ in that motor characteristics are more evident and appear earlier in PD than in DLB.

Although amyloid beta 1–42 is linked to Alzheimer's disease (AD) and its pathology, new research suggests that this biomarker may also predict cognitive loss in Parkinson's disease (PD). These findings are in accordance with prior study, which shown that AD pathology leads to cognitive impairment in Parkinson's disease and may be useful in forecasting cognitive decline.

Inflammation's function in the pathophysiology of Parkinson's disease is also being investigated, particularly the impact of cytokines and other mediators. Inflammatory reactions resulting from dopaminergic neuron loss may have a role in the aetiology of Parkinson's disease. Microglia and astrocyte activation in response to damaged dopaminergic neurons has been demonstrated in vitro.

To summarize, Parkinson's disease is a complicated neurodegenerative illness involving a variety of molecular pathways, all of which may be involved in the disease's neuropathophysiology.

Diagnosis

A thorough history and physical examination should be included in the differential diagnosis of Parkinson's disease. Cases that are difficult or unclear should be

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referred to a movement disorder expert for additional examination. Because there are no definitive tests to confirm the diagnosis of PD, a physician must evaluate the patient's history, assess symptoms, and rule out other illnesses such as multiple-system atrophy, DLB disease, and essential tremor before making a clinical diagnosis. A 4-Hz to 6-Hz resting tremor, "cogwheel" stiffness, and bradykinesia are the "classical trinity" of motor characteristics of Parkinson's disease. These key characteristics are frequently described as the disease's earliest clinical manifestations. Postural instability is a fourth symptom that affects around 50% of PD patients within five years of diagnosis. Despite the fact that Parkinson's disease is thought to be a disease of the elderly, several genetic variations have been found in younger people. Clinically, younger people (under 60 years old) may have less stiffness and bradykinesia, which might lead to a missed or delayed diagnosis.

Because it is one of the few reversible causes of PD, drug-induced parkinsonism (DIP) should be included in the differential diagnosis. In order to prevent treating patients improperly, it is critical to identify DIP, which demands a full pharmacological review in all patients suspected of having PD. Elderly women, patients with various comorbidities, and patients taking several drugs at high doses for long periods of time are all at risk for DIP.[11]

Because there are so many etiologies for olfactory abnormalities, olfactory screening may be helpful in detecting PD, but it should not be regarded a diagnostic tool in and of itself. In the future, protein markers from biopsy or other procedures, such as spinal fluid, rectal, salivary gland, and intestinal samples, might be used. Imaging methods are generally employed to rule out other neurological conditions in the diagnosis of Parkinson's disease; for example, magnetic resonance imaging (MRI) can be used to detect normal-pressure hydrocephalus. Using 7-T MRI to examine the structure of the substantia nigra (SN) might be a future diagnostic approach for identifying people with PD. Dopamine transporter scans (DaT scans) can help distinguish between LB-type dementias (PD and DLB) and non-LB dementias like Alzheimer's. Because of a lack of clarity on which populations to test, the repercussions of the test results, and cost difficulties, the use of genetic testing in diagnosing PD is still controversial.[12]

Clinical Feature

Tremor at rest, rigidity, akinesia (or bradykinesia), and postural instability are the four cardinal signs of Parkinson's disease (PD). Furthermore, flexed posture and freezing (motor blocks) have been added to the list of characteristic signs of parkinsonism, with Parkinson's disease (PD) being the most frequent type. Motor and non-motor impairments should be examined in the context of each patient's demands and aspirations, due to the various profiles and lifestyles of persons afflicted by PD.

Bradykinesia

Bradykinesia, or slowness of movement, is the most common clinical sign of Parkinson's disease, while it can also be observed in other illnesses, such as depression. Bradykinesia is a symptom of basal ganglia dysfunction that includes problems planning, starting, and executing movement as well as completing sequential and simultaneous activities. 22 Slowness in doing everyday chores, as well as delayed movement and reaction times, are common symptoms. This might include issues with tasks that need fine motor control (eg, buttoning, using utensils). Lack of spontaneous motions and gestures, drooling due to poor swallowing, monotone and hypo phonic dysarthria, loss of facial expression (hypomania) and decreased blinking, and diminished arm swing when walking are all symptoms of bradykinesia. Because bradykinesia is one of the most commonly recognized signs of Parkinson's disease, it may be seen prior to a thorough neurological evaluation. Patients with bradykinesia are frequently asked to execute quick, repeated, alternating hand (finger taps, hand grips, hand pronation–supination) and heel taps, with the amplitude not just slowing but also decreasing.[13]

Tremor

The most frequent and easily recognized sign of Parkinson's disease is rest tremor. Tremors are unilateral, with a frequency of 4–6 Hz, and are virtually usually felt in the distal region of an extremity. Supination–pronation ("pill-rolling") tremors pass from one hand to the other are known as hand tremors. In individuals with Parkinson's disease, rest tremor can also affect the lips. Patients who present with head tremor are more likely to have essential tremor, cervical dystonia, or both, rather than Parkinson's disease. Rest tremor usually goes away when you do anything or when you sleep. Some patients may describe "internal" shaking that isn't accompanied by a tremor. A number of characteristics distinguish the tremor of Parkinson's disease from those of essential tremor.

Some people with Parkinson's disease have a history of postural tremor, which is phenomenologically equivalent to essential tremor, for years or even decades before developing parkinsonian tremor or other PD-related symptoms. We and many others have contributed to a growing body of evidence indicating essential tremor is linked to Parkinson's disease.[14]

Rigidity

Rigidity is defined by increased resistance, which is often accompanied by the "cogwheel" phenomena, especially when paired with an underlying tremor, and is evident throughout a limb's range of passive movement (flexion, extension or rotation about a joint). It can occur both proximally (neck, shoulders, hips) and distally (arms, legs, and feet) (eg, wrists, ankles). The Froment's procedure, which involves voluntary motions of the contralateral limb, frequently increases stiffness and is particularly beneficial in diagnosing moderate instances of rigidity.

Postural deformities

Axial stiffness (neck and trunk rigidity) may also develop, resulting in aberrant axial postures (eg, anterocollis, scoliosis). Rigidity is commonly accompanied with postural abnormalities that result in flexed neck and trunk posture, as well as flexed elbows and knees. Flexed posture, on the other hand, usually appears later in the disease. Some individuals may acquire striatal limb abnormalities (e.g., striatal hand, striatal toe). Striatal wrists and ankles have ulnar deviation, flexion of the metacarpophalangeal joints, extension and flexion of the proximal and distal interphalangeal joints, and toe extension or flexion. In one study, striatal toe (big toe extension) was found in 21% of individuals with clinically diagnosed Parkinson's disease. Patients with striatal irregularities are more likely to be younger and to develop parkinsonian symptoms sooner. [15]

Postural instability

Postural instability caused by a lack of postural reflexes is a symptom of late-stage Parkinson's disease that usually appears after the beginning of other clinical symptoms. To evaluate the degree of retropulsion or propulsion, the pull test is employed, in which the patient's shoulders are quickly moved backward or forward to measure the degree of retropulsion or propulsion. Taking more than two steps backwards or having no postural response at all is considered an abnormal postural reaction. The most prevalent cause of falls (together with gait freezing) is postural instability, which increases the risk of hip fractures substantially.[16]

Freezing

Freezing, also characterized as motor blocks, is a kind of akinesia (lack of movement) that is one of the most debilitating symptoms of Parkinson's disease. Although freezing is a common symptom of Parkinson's disease, it does not occur in all cases. According to replies from 6620 patients to a questionnaire submitted to 12 000 members of the German Parkinson Association, 47 percent of patients experienced freezing; it happens more frequently in males than in women, and less commonly in patients who had tremor as their primary symptom. The legs are the most usually affected by freezing when walking, although the arms and eyes can also be affected. It usually presents as a brief incapacity to move (usually less than 10 seconds). This might involve a sudden inability to move the feet in certain conditions or hesitancy while starting to walk (start hesitation) (eg, turning or walking through a narrow passage, crossing busy streets, approaching a destination). Patients who are frozen suffer significant social and clinical effects. It is a common cause of falls in particular.[17]

Cerebrospinal Fluid (CSF) and Blood Tests

There is currently no clinically relevant CSF-based diagnostic for the diagnosis of Parkinson's disease. Several investigations have looked at the amounts of proteins in CSF (for example, the levels of distinct -synuclein species),

but the tests' sensitivity and specificity have been low. Though a lower Apo lipoprotein A1 level in the blood corresponds with a greater severity of motor symptoms, its value as a blood biomarker has yet to be proved. The lack of strong biomarkers with high sensitivity and specificity to detect the illness in the early or even prodromal stages is a major hurdle in PD research, and no single measure presently meets all of the requirements for a biomarker in PD. If individuals are detected and treated during this prodromal stage, disease-modifying medicines will be most successful. RBD detected by polysomnography and olfactory impairment determined by established procedures, such as the University of Pennsylvania's scent recognition test, are two possible clinical indicators.[17]

Pharmacologic management

The primary goal of Parkinson's disease research is to discover disease-modifying therapies that can reduce or stop the progression of the illness. However, no definite disease-modifying medication exists to achieve this goal.

Dopaminergic therapy

Once patients acquire functional impairment, the American Academy of Neurology (AAN) suggests starting one of the current pharmacological regimens. Some medical interventions for motor symptoms include levodopa/carbidopa, dopamine agonists (both ergot and non-ergot types), monoamine oxidase-B (MAO-B) inhibitors, intravenous dopamine agonist (apomorphine), catechol-O-methyltransferase (COMT) inhibitors, N-methyl-D-aspartate (NMDA) receptor inhibitors, and anti-cholinergics. In the latter stages of Parkinson's disease, additional channels can help with drug delivery (e.g., intrajejunal infusions, subcutaneous injections or transdermal patches). If the patient's motor fluctuations and dyskinesias persist, deep brain stimulation may be an option (DBS). In the treatment of bradykinesia and stiffness, dopaminergic medication is extremely efficient, but monoamine MAO B inhibitors are only somewhat effective. Levodopa and dopamine agonists aid to slow disease progression and impairment. Tremor responds to anticholinergic medications like trihexyphenidyl, however dopamine replacement treatment has a poor and unpredictable effect.[18]

Levodopa and Novel Levodopa Formulations

The death of dopaminergic neurons in the SNpc causes striatal dopamine depletion, which causes severe motor symptoms in PD. The use of levodopa to replace striatal dopamine was a key advance in the treatment of Parkinson's disease, and several other targets for dopaminergic treatments have been discovered since then. Levodopa is regarded gold standard therapy, and practically every patient will require it at some point throughout their disease.

Bioavailability of levodopa can be increased by producing more effective oral formulations (e.g., prolonged release formulations) or designing novel administration ways (e.g.,

intestinal infusion, transcutaneous administratin via mini pumps or by inhalation). RYTARY/IPX066 is a new oral formulation of levodopa-carbidopa (LD/CD) that combines immediate-release and extended-release LD/CD.

Although levodopa provides the most symptomatic relief, MAO-B inhibitors/dopamine agonists can be used as a first-line treatment to prevent further problems. A randomised study of newly diagnosed PD patients found that levodopa sparing treatment had no long-term effect. However, as patients, this study has limitations, such as a lack of generalizability.

Dopamine agonists

The D2 receptor family is primarily targeted by dopamine receptors. Ergoline derivatives were the first members of this medication class. Non-ergoline medicines, such as pramipexole, ropinirole, apomorphine, piribedil, and rotigotine, have all been utilised to address cardiac and pulmonary safety issues. When administered as initial monotherapy, dopamine agonists cause less pulsatile striatal dopamine receptor activation than levodopa and can significantly minimise the likelihood of motor problems.

MAO B inhibitors

Inhibition of MAO B results in an increase in synaptic dopamine levels as well as symptomatic efficacy. Since the 1970s, selegiline, a selective irreversible MAO B inhibitor, has been used as a supplement to levodopa. The MONOCOMB research found that selegiline monotherapy slowed the course of early-stage Parkinson's disease. Selegiline demonstrated levodopa-sparing properties in advanced Parkinson's disease and was well tolerated over time. Selegiline treatment significantly lowered UPDRS part I, II, and III scores in a recent study in Japanese patients with early PD. Safinamide is an antiglutaminergic MAOB inhibitor that is reversible. In advanced Parkinson's disease, safinamide improves quality of life by improving control of motor symptoms. Safinamide, when administered as an addition to levodopa, enhanced ON time without inducing bothersome dyskinesias and decreased the occurrence of the 'wearing off' phenomena in a recent randomised control experiment.[19]

Catecohol-O-methyl transferase (COMT) inhibitors

To avoid peripheral dopamine metabolism, current levodopa formulations incorporate carbidopa or benserazide, which increases the bioavailability of the former medicine. This switches levodopa metabolism from the peripheral to a secondary route including COMT. Inhibition of the COMT route will boost levodopa's bioavailability and half-life, which will benefit patients with motor irregularities.Triple treatment with levodopa, carbidopa, and a COMT inhibitor enhances ON time, decreases OFF time, and improves quality of life considerably.[20]

Non-dopaminergic Pharmacological Targets

Late-stage Parkinson's disease symptoms (both motor and nonmotor) do not respond well to dopaminergic treatment. Anomalies in non-dopaminergic neurotransmitters like as acetylcholine, glutamate, norepinephrine, or serotonin might be the cause. Non-dopaminergic drugs are used to treat symptoms such as motor fluctuations, levodopa-induced dyskinesias, gait freezing, postural instability and falls, treatment-resistant tremor, swallowing and speech problems, and treatment-resistant tremor. Degeneration of cholinergic neurons causes acetylcholine insufficiency, which causes dementia, gait problems, and falls. The trial of donepezil for the treatment of falls is based on the theory that PD patients have an aberrant cholinergic system that causes them to fall frequently. Rivastigmine, a cholinesterase inhibitor, is used to treat dementia caused by Parkinson's disease. The effectiveness of rivastigmine in the treatment of gait irregularities and frequent falls is currently being investigated.[21-22]

Tyrosine kinase inhibitors for the treatment of PD

Abelson non-receptor tyrosine kinase (C-Abl) levels and activation were recently shown to be elevated in the brain tissue of individuals with Parkinson's disease. C -Abl inhibitors that are brain permeable might be used to treat Parkinson's disease and other neurodegenerative diseases.[23-25]

Surgical treatment

Deep brain stimulation (DBS) of the sub thalamic nucleus (STN) or globus pallidus interna (GPI) is a well-known treatment for people with movement impairments. Thalamic DBS is a potential alternative for treating tremors. When motor fluctuations and dyskinesias become problematic despite the fact that the motor symptoms are responsive to levodopa, surgical therapy is chosen. The typical time it takes for DBS to be done once a Parkinson's disease diagnosis is established is roughly 10–13 years. The EARLYSTIM study, a multicenter randomized control trial, found that DBS was effective in the early stages of illness.

Exercise, education, support groups, speech therapy, and diet are all non-pharmacological treatments for Parkinson's disease. Evidence from the literature suggests that they should be used early in the course of the disease.[26]

CONCLUSION

Parkinson's disease is one of the most prevalent neurodegenerative illnesses affecting the elderly, and it's linked to higher morbidity and death rates. For the best case management, it is vital to be aware of the illness symptoms, therapies, and the disease's long-term progression. The neuropathology of Parkinson's disease and its development across the nervous system have made tremendous progress. None of these therapies, however, are curative. Because of the severity of treatment-resistant

motor issues and non-motor symptoms, PD remains a progressive condition that eventually causes severe impairment. The primary unmet needs to be addressed by present and future research efforts include modifying variables that contribute to disease development and further postponing impairment.

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