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Understanding the Advancement in Parkinson's Disease

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ABSTRACT

Parkinson's disease is the second commonest neurodegenerative disorder, after Alzheimer's, and represents a major cause of neurological morbidity globally. The diagnosis is made clinically and management is currently restricted to symptomatic treatments, with levodopa continuing to form the cornerstone of pharmacological therapy. Deep brain stimulation of specific basal ganglia targets can offer significant symptomatic benefits in selected patient groups. To date, no established disease-modifying agents that can halt or reverse the underlying neurodegenerative process are available in clinical practice. This article aims to provide an overview, and an update, on the diagnosis and management of Parkinson's disease.

INTRODUCTION:

DEFINITION: Parkinson's disease (PD) is a neurodegenerative disorder that affects predominately dopamine-producing (dopaminergic) neurons in a specific area of the brain called substantia nigra. Symptoms develop gradually and differ from one person to another due to the diversity of the disease. People with PD may experience-

•Tremors, mainly at rest and described as a pill-rolling tremor in hands.

•Bradykinesia

•Limb rigidity

•Gait and balance problems

STAGES OF PARKINSONISM

Parkinson's disease (PD) impacts people in different ways. No everyone will experience all the symptoms of Parkinson's, and if they do, they won't necessarily experience them in quite the same order or at the same intensity. There are typical patterns of progression in Parkinson's disease that are defined in stages.

Stage One-During this initial stage, the person has mild symptoms that generally do not interfere with daily activities. Tremors and other movement symptoms occur on one side of the body only. Changes in posture, walking, and facial expression occur.

Stage Two- Symptoms start getting worse. Tremors, rigidity, and other movement symptoms affect both sides of the body. Walking problems and poor posture may be apparent. The person is still able to live alone, but daily tasks are more difficult and lengthier.

Stage Three-Considered mid-stage, loss of balance, and slowness of movement are hallmarks. Falls are more common. The person is still fully independent, but symptoms significantly impair activities such as dressing and eating.

Stage Four-At this point, symptoms are severe and limiting. It's possible to stand without assistance, but movement may require a walker. The person needs help with activities of daily living and is unable to live alone.

Stage Five-This is the most advantageous and debilitating stage. Stiffness in the legs may make it impossible to stand or walk. The person requires a wheelchair or is bedridden. Around the clock nursing care is required for all activities. The person may experience hallucinations and delusion. The Parkinson's community acknowledges that there are many important nonmotor symptoms as well as motor symptoms.

RATING SCALE

Doctors may refer to a scale to help them understand the progression of the disease. Parkinson's stages correspond both to the severity of movement symptoms and to how much the disease affects a person's daily activities. The most commonly used rating scales focus on motor symptoms. They are the-

• Rates symptoms on a scale of 1to5. On this scale, 1 and 2 represent early stages, 2 and 3 mid-stage, and 4 and 5 advanced-stage Parkinson's. (Hoehn and Yahr stages)

• Accounts for cognitive difficulties, ability to carry out daily activities, and treatment complications. (Unified Parkinson's Disease Rating Scale- UPDRS)

YOUNG ONSET PARKINSON'S

Young-onset Parkinson's disease (YOPD) occurs in people younger than 50 years of age. Most people with idiopathic, or typical, PD develop symptoms at 50 years of age or older. YOPD affects about two to 10 percent of the one million people with PD in the United State. Symptoms are similar to late-onset PD but it is important to understand the challenges YOPD individuals often face at financial, family and employment levels. In rare instances, Parkinson s-like like symptoms can appear in children and teenagers. This form of the disorder is called juvenile Parkinsonism and is often associated with specific, high PD risk genetic mutation.

How is young-onset PD different?

People diagnosed with YOPD have a more frequent family history of Parkinson's disease and longer survival. People living with young-onset PD may experience.

• Slower progression of PD symptoms

• More side effects from dopaminergic medication

• More frequent dystonia's such as the arching of the foot

TYPES OF PARKINSONISM

Parkinson's is a term used to describe the collection of signs and symptoms found in Parkinson's disease (PD). These include slowness, stiffness, tremor, and imbalance. Conditions other than PD may have one or more of these symptoms, mimicking Parkinson's.

Multiple Symptoms Atrophy (MSA)

• MSA is a term encompassing several neurodegenerative disorders in which one or more symptoms in the body deteriorate.

• Initially, it may be difficult to distinguish MSA from Parkinson's. More rapid progression, poor response to common PD medication, and development of other symptoms in addition to Parkinsonism may be clues.

• The diagnosis of MSA is made based on clinical features. There is no specific test that provides a definitive diagnosis.

• There is no specific treatment for MSA. Treatment focuses on alleviating symptoms.

• People with MSA usually respond poorly to PD medication and may require higher doses than the typical person with PD, often with only modest benefits.

Progressive Supranuclear Palsy (PSP)

• Most common degenerative type of atypical Parkinsonism.

• Symptoms tend to progress more rapidly than PD. People with PSP may fall frequently early in the course of the disease. Later symptoms include limitation in eye movements, particularly looking up and down, which also contributes to falls.

• The diagnosis of PSP is made based on clinical features. There is no specific test that provides a definitive diagnosis.

•There is no specific treatment for PSP. Treatment focuses on alleviating symptoms.

Corticobasal Syndrome (CBS)

• CBS is the least common of the atypical causes of Parkinsonism.

• Usually begins with symptoms affecting one limb. In addition to Parkinsonism, other symptoms can include abnormal posture of the affected limb, fast, jerky movement, difficulty with some motor tasks despite normal muscle strength, difficulty with language among others.

• Supportive treatment such as botulinum toxin for dystonia, antidepressants, speech, and physical therapy may be helpful. Levodopa and dopamine agonists seldom help.

Dementia with Lewy bodies (DLB)

• DLB is a progression, neurodegenerative disorder in which abnormal deposits of a protein called alpha-synuclein build up in multiple areas of the brain.

• DLB is second to Alzheimer's as the most common cause of degenerative dementia that first causes progressive problems with memory and fluctuations in thinking, as well as hallucinations. These symptoms are joined later in the course of the disease by Parkinsonism with slowness, stiffness, and other symptoms similar to PD.

• While the abnormal protein is found in the brains of those with PD, when an individual with PD develops memory and thinking problems it tends to occur later in the course of the disease.

• There are no specific treatments for DLB. Treatment focuses on symptoms.

Drug-Induced Parkinsonism

• This is the most common form of secondary Parkinsonism.

• Side effects of some drugs, especially those affecting brain dopamine levels (antidepressants or antipsychotic medications), can cause Parkinsonism.

• Medication that can cause the development of Parkinsonism include:

▫ Antipsychotic

▫ Certain antiemetic (anti-nausea medication)

▫ Some antidepressants

▫ Reserpine

▫ Tetrabenazine

▫ Some calcium channel blockers

▫ Usually after stooping those medications Parkinsonism gradually disappears over weeks or months, though symptoms may last for up to a year.

Vascular Parkinsonism (VP)

• There is some evidence that multiple small strokes in key areas of the brain may cause Parkinsonism.

• NO specific clinical features or diagnosis tests reliably differentiate PD and vascular Parkinsonism, though some features may suggest VP.

• Other signs that can indicate VP include- evidence of vascular disease on an MRI of the brain in combination with varying levels of deterioration, prominent early cognitive problems and lower body issues, such as early gait and balance problems.

• Dopaminergic medication like levodopa may possibly has modest benefits, depending on the location of vascular disease in the brain.

CONDITIONS RELATED TO PARKINSON'S

No two people have the same Parkinson's disease (PD). With diverse symptoms and varied speed of progression, PD does not affect every person the same way.

Melanoma- It is an invasive form of skin cancer that has been found to develop more often in people with Parkinson's. Early detection of melanoma means the chance of stopping cancer from progressing to the lymph nodes. Other risk factors for melanoma are male gender, Caucasian race, constant exposure to ultraviolet light and family history of melanoma.

Neurogenic Orthostatic Hypotension (nOH)

Orthostatic hypostatic (OH) is a persistent drop in the blood pressure that occurs upon moving from sitting to standing or from lying down to standing up or sitting. Doctors define it as a blood pressure drop of 20 millimeters of mercury (20 mm Hg) in systolic blood pressure or a drop of 10 millimeters in diastolic blood pressure. Certain medications, dehydration, and condition such as heart disease increase this risk.

When OH happens in people with PD or other nervous system disorders, it is called 'neurogenic OH (nOH)'. Damage caused by these disorders, including PD, can result in the nervous system not being able to make or release norepinephrine- a chemical that constricts blood vessels and raises blood pressure. This causes dizziness or lightheadedness. This range of people affected by nOH is large; estimates suggest anywhere from 10 to 65 percent of people with PD develop nOH.

Pseudobulbar Affect (PBA)

Pseudobulbar affect is characterized by frequent, uncontrollable outbursts of crying or laughing. It happens when a nervous system disorder, such as PD, affects the brain areas controlling expressions of emotions. This disrupts brain signaling and triggers involuntary episodes. Outbursts are usually brief, though they can be intense and may occur several times per day. PBA is often mistaken for depression or bipolar disorder. The episodes often do not match the situation or the person's feelings. You may be happy about something but start sobbing, or laugh in an inappropriate situation. PBA used to be referred to as "emotional incontinence" or "pathological laughing or crying".

BRAIN DONATION

There is a great shortage of brain tissue for the study of many neurodegenerative disorders, including Parkinson's disease (PD). Brain donation gives an opportunity for researchers to have a greater view on neurodegenerative disorders and provide insights on improving treatments and medications while increasing the odds of finding a cure.

Why should I donate my brain to Parkinson's researchers?

Due to our aging global population, each year more people are being diagnosed with neurological disorders. Breakthroughs in brain disease depend on studies using donated post mortem human brain tissue. Since one brain can provide tissue for dozen sometimes hundreds of neurological studies, an individual brain donation is a highly valuable gift that almost anyone can make.

The Future of Brain Imaging in Parkinson's disease is a brain disorder with distinct molecular, function, and structural features. These characteristics make it a prototypical neurological disorder where new neuroimaging techniques, especially the combination of multiple techniques in single patients, have the potential to make significant contributions to clinical practice.

Functional imaging-Imaging of brain activity can be done with functional magnetic imaging (fMRI) or positron emission tomography (PET). These approaches have made significant contributions to our understanding of the pathophysiology of PD. The field has grown from focusing on abnormal, known to occur in PD. If clinical validated, such approaches may be helpful for diagnosis and disease monitoring.

Structural imaging- Structural imaging in PD has made important advances over the past decade, and as we look to the future several important themes emerge. The **first theme** is high-field imaging and improved spatial resolution having a significant impact on visualizing and quantifying features of the basal ganglia and other regions going forward. The **second theme** is in linking diffusion imaging as a biomarker of differential diagnosis, progression of PD, and relation to pathology. Recent evidence has linked diffusion imaging as a predictor of both cognitive function and motor symptoms in PD.

Nuclear imaging- A major unsolved problem is the lack of a specific imaging marker for the pathological hallmark of PD, alpha-synuclein aggregates. Other fields of development in nuclear imaging include- surface receptor-ligand which are sensitive to synaptic levels of transmitters.

AETIOLOGY OF PARKINSON'S

In an area of your brain called the substantia nigra, cells that make the chemical dopamine starts to die. Dopamine has an important job to do. It acts like a messenger that tells another area of your brain when you want to move a part of your body, when the cells that make dopamine start to die, your dopamine level drops. When it gets too low, you can't control your movement as well and start to get Parkinson's symptoms. No one knows what triggers the death of those cells. Scientists think it's your genes and environment working off of each other in a way we don't understand.

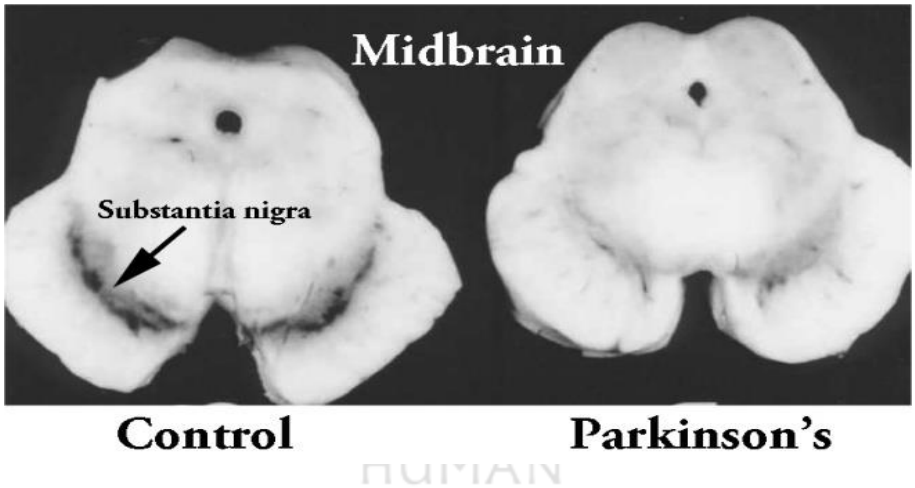

Figure No. 1: Aetiology of Parkinson's

What Role Do Genes Play?

Your genes are like your body's instruction book. So, if you get a change in one of them, it can make your body work in a slightly different way. Sometimes, that means you're more likely to get a certain disease. Several genetic mutations can raise your risk for Parkinson's each by a little bit. They have a part in about 1in 10 cases. If you have one or more of these changes, it doesn't mean you'll get Parkinson's some people will, but many won't, and doctors don't know why. It may have to do with other genes or something in your environment.

Can Parents Pass Parkinson's to their kids?

They can, but it's rare and only affects a small number of families. About 1in 100 people with Parkinson's get it this way.

How Does Environment come into it?

Your environment is a hard one to pin down. Partly, that's because it covers a lot of ground. It's everything that's not your genes, which could mean where you live, what you eat, chemicals you've come into contact with, and more. Not only that, but it could take years for the effects from something in your environment to show up. So, for, doctors have a lot of clause but no smoking gun. So, you could have people who live or work in an area around chemicals tried to Parkinson's, but many of them don't get it.

Some research shows links between Parkinson's and:

● Agents orange, a chemical used to destroy trees and crops in the Vietnam War.

● The certain chemical used in farming, such as insecticides, herbicides, and fungicides.

● Some metals and chemicals used in factories, such as manganese, lead, and trichloroethylene (TCE).

These can come into play based on where you live, what you do for work, or if you served in the military. Sometimes, these chemicals seep into well water, so that's one more way they can affect you.

What raises someone's Risk for Parkinson's? It's a complex picture, but you may be likely to get Parkinson's based on

Age- Since it mostly affects people 60 and older, your risk goes up as the year goes by.

Family history- If your parent, brother, or sister has it, you're a little more likely to get it.

Job- Some types of work, like farming or factory jobs, can cause you to have contact with chemicals linked to Parkinson's.

Race- It shows up more often in white people than other groups.

Serious head injury- If you hit your head hard enough to lose consciousness or forget things as a result of it, you may be more likely to get Parkinson's later in life.

Gender- Men get it more than women. Doctors aren't sure why.

Where you live- People in the rural area seem to get it more often, which may be tied to chemicals used in farming.

What Else Do We Know?

As scientists try to learn what's at the root of Parkinson's, they're looking far and wide to pick up clues where they can. They've found that people with Parkinson's tend to have something called Lewy bodies in their brain. These are unusual clumps of a protein called alpha-synuclein. The protein itself is normal, but the clumps are not. And they're found in parts of the brain that affect sleep and sense of smell, which could explain some symptoms of Parkinson's not related to movement. Your gut also has a part in it, as some of its cells make dopamine, too. Some doctors think that might be where the earliest signs of show up, but that idea needs more research.

CONCLUSION

The etiology of Parkinson's disease (PD) has long been thought to involve both genetic and environmental factors, but until recently there has been no direct evidence to support either one as a causative factor. However, in the past 8 years six different genes have been identified as causing familial PD. Together, they support the notion that common pathogenetic mechanisms exits across the etiology spectrum of PD, specifically, mutations in α-synuclein, parkin, UCHL1, DJ1, PINK1, and LRRK2 cause PD, with a Mendelian pattern of inheritance. DJ1 and PINK1 are mitochondrial protein and overexpression of α-synclein and parkin induce mitochondrial defects. These same proteins are involved in the response to oxidative stress and affect proteasomal function. In contrast, few environmental factors can cause nigrostriatal call death to appear to interact by interfering with mitochondrial function, inducing oxidative stress, and modifying proteasomal function. Therefore, common themes are beginning to emerge in the etiopathogenesis of PD. This bodes well for research focused on the development of a treatment that will modify the course of PD.

SIGNS AND SYMPTOMS

Motor symptoms, Postural Instability, and Gait

In Parkinsonism disease, the loss of dopaminergic call in the substantia nigra affects the basal ganglia's ability to coordinate inhibitory and excitatory neural motor signals. The net effect is an overall reduction in motor output, referred to as hypokinesia. Unfortunately, drugs used to treat PD can introduce too much dopamine, causing over-activation of the motor system and producing dyskinesias. The motor symptoms associated with PD affect all aspects of daily activities, gait, postural stability, and mobility.

Tremor, rigidity, bradykinesia, and dyskinesia Tremor typically begins on one side of the body with a tremor rate of 3 to 7 cycles per second. Tremors are usually less severe or even absent with voluntary movement and can increase during times of emotional stress. Tremors are considered one of the cardinal symptoms of Parkinson's disease as in 80 percent of patients with autopay-proven.

Rigidity is another common visible motor symptom associated with PD. It is a type of increased muscle tone generally defined as increased resistance to passive movement of a joint. Rigidity tends to be more prominent in the flexor muscles of the trunk and limbs, causing a characteristic stopped posture. There are two types of rigidity- lead pipe and cogwheel. Lead pipe rigidity is defined as a constant resistance to motion throughout the entire range of movement. Cogwheel rigidity refers to resistance that stops and starts as the limb is moved through its range of motion.

Bradykinesia, another cardinal motor feature of PD, is of unknown cause and remains the subject of debate. It is defined as slowed voluntary movements such as arm and leg swing during gait. One of the striking clinical characteristics of bradykinesia is its variability, with the same patient being able to achieve perceivable different movement speeds in different contexts. An extreme manifestation of this variability is kinesia paradoxica, in which patient are suddenly able to move at near-normal speed, that can occur in extreme, aversive contexts.

Dyskinesia consists of abnormal movements as the movement of neck, head, limbs etc which are debilitating, physically tiring, and embarrassing. Several reports have shown that the rate of this problem varies, ranging from 19% to 80% in PD patients.

Balance, Orientation, and Postural Control

Balance is the ability to automatically and accurately maintain your center of mass over your base of support. Postural orientation is the ability to control the segments of your body with one another and to gravity, taking into account the environment and whatever task is being performed. Postural control involves both balance and postural orientation. Poor balance and unstable posture are commonly observed motor symptoms in those with PD. Until recently, it was thought to occur relatively late in the course of the disease. This is reflected by the Hoehn and Yahr scale, in which postural instability is represented only in the advanced stages of the disease. However, there are early stages of Parkinson's and, although there is fluctuation, generally increase over time.

Gait Impairment

Gait changes are a hallmark of PD, with reductions in speed, decreased step length, altered cadence, and increased gait variability. While gait abnormalities are not pronounced in the early stages, their prevalence and severity increase with disease progression. Within 3 years of diagnosis, more than 85% of people with clinical probable PD develop gait problems. The potential consequences of gait impairments in PD are significant and include increased disability, increased risk for falls, and reduced quality of life.

In kinematic studies of those with Parkinson's disease, these gait alterations are commonly observed-

▫Lack of heel strike- foot lands either flat or forefoot lands first

▫Incomplete knee extension during stance phase

▫Inability to extend the knee and flex the ankle in terminal stance

▫Forward trunk lean

▫Lack of motion in the trunk

▫Reduced or absent arm swing

▫Reduced speed and amplitude

Diagnosis of Parkinson's

There is "one way" to diagnose Parkinson's disease (PD). However, there are various symptoms and diagnostic tests used in combination. Making an accurate diagnosis of Parkinson's particularly in its early stages is difficult, but a skilled practitioner can come to a reasoned conclusion that it is PD. It is important to remember that two of the four symptoms must be present over some time for a neurologist to consider a PD diagnosis.

● Shaking or tremor

● Slowness of movement, called bradykinesia

● Stiffness or rigidity of the arms, legs or trunk

● Trouble with balance and possible falls, also called postural instability

Often, a Parkinson's diagnosis is first made by an internist or family physician. Many people seek an addiction opinion from a neurologist with experience and specific training in the assessment and treatment of PD referred to as a movement disorder specialist.

Testing for Parkinson's disease no lab or imaging test is recommended or definitive for Parkinson's disease. However, in 2011, the U.S Food and drug Administration approved an imaging scan called the DaT scan. This technique allows doctors to see a detailed picture of the brain dopamine system.

A DaT scan involves an injection of a small amount of a radioactive drug and a machine called a single-photon emission computed tomography (SPECT) scanner, similar to an MRI.

The drug binds to dopamine transmitters in the brain, showing where in the brain dopaminergic neurons are. The results of a DaT scan show that you have Parkinson's, nut they can help your doctor confirm a diagnosis or rule out a Parkinson's mimic.

Is Early Diagnosis Possible? Experts are becoming more aware of symptoms of Parkinson's that precede physical manifestations. Clues to the disease that sometimes show up before motor symptoms and before a formal diagnosis are called prodromal symptoms. These include the loss

of sense of smell, sleep disturbance called REM behavior disorder, ongoing constipation that's not otherwise explained and mood disorders, such as anxiety and depression.

Biomarkers for PD

Biomarkers are biologic indicators of disease or therapeutic effects that can be measured by in vivo biomedical or molecular imaging as well as laboratory methods. Biomarkers can include changes in body chemistry or physiology or changes in a person's behavior may be a biomarker. Currently, there are no proven biomarkers for Parkinson's disease. Biomarkers are used, however, in the successful detection of many other diseases.

Finding a biomarker that aids in the early detection of PD may provide information about the cause of PD and its progression, and lead to treatments that delay the progression of the disease. As with any biomarker, one for PD must be specific for Parkinson's disease and sensitive to every person who has the disease. A good PD biomarker should identify someone who is beginning to undergo metabolic changes associated with PD before substantial injury has occurred. It should measure disease activity and progression and assist in determining the benefit of treatments and neuroprotective therapies.

The range of potential biomarkers for Parkinson's is vast, and there have been some promising leads. For example, researchers are investigating the use of noninvasive imaging to detect changes in brain function or brain biochemistry. This is a promising area for research because several studies have tentatively linked PD with changes in proteins or other molecular in blood, urine, or the cerebrospinal fluid.

There is a pressing need for an accurate, relatively noninvasive, and affordable PD diagnosis test or biomarker. This is particularly true given widespread recognition that early detection and early treatment helps to slow the progression of the disease, minimize symptoms, and improve the patient's overall quality of life. Currently, there is no one imaging technique or test that can provide a conclusive primary diagnosis of PD. There are also no laboratory tests utilizing blood, cerebrospinal fluid, or urine sample that have proven to be effective in primary diagnosis or confirmation of PD.

Imaging Biomarkers

Functional imaging techniques such as positron emission tomography (PET) and single-photon computed emission tomography (SPECT) can support the diagnosis of PD but are usually limited to a research setting. Computed tomography (CT) and magnetic resonance imaging (MRI) brain scans of people with PD usually appear normal.

Current imaging techniques are used mostly to exclude other diseases, such as basal ganglia tumors, vascular pathology, and hydrocephalus. A specific technique, diffusion MRI, has been reported to be useful at discriminating between typical and atypical Parkinson's although its exact diagnostic value is still under investigation.

Two widely-used imaging techniques, fluorodopa PET and DaT scan focus on dopamine, using radiotracers to measure dopamine function in the basal ganglia. Unfortunately, dopamine biomarkers only detect changes in dopamine after the disease is well established. A substantial fraction of patients with early idiopathic Parkinson's disease has normal scans, and the costs and use of intravenous radioactive tracers are seen as an addition to these two types of scan, transcranial sonography is showing promise as a diagnostic tool.

Fluorodopa PET Scan

Fluorodopa (FDOPA) is a fluorinated form of L-dopa that tis synthesized for use as a radiotracer in PET scan. Current studies employing the use of FDOPA PET scanning have focused on analyzing the efficiency of neurons in the striatum that utilize dopamine. This test is useful in distinguishing PD from other types of neurodegeneration.

These pictures below are examples of a PET scan that has utilized fluorodopa as a radiotracer. The bright orange areas in the scan on the left show a robust uptake of fluorodopa in the striatum indicating normal dopamine function. The image on the right shows much less uptake of the fluorodopa, indicating a significant loss of dopamine receptors in a person with PD.

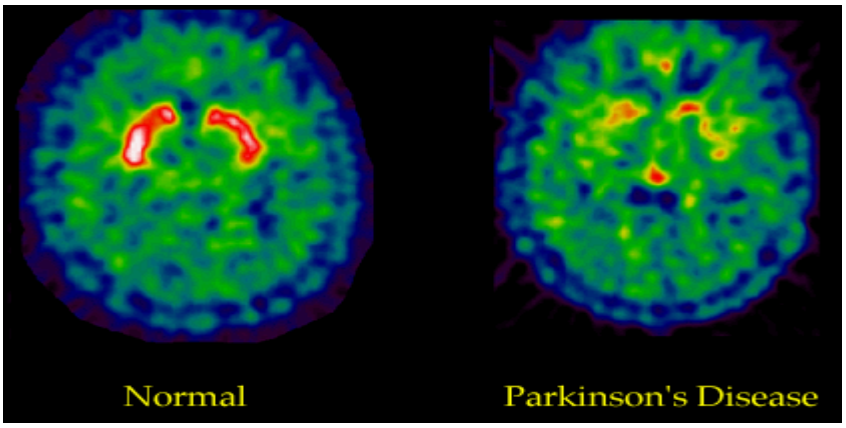

Figure No. 2: Fluorodopa PET Scan

DaT scan

DaT (dopamine transporter) imaging scan looks at the function of presynaptic dopamine transporters. The DaT scan technique has the potential to predict the course of the disease by measuring the number of dopamine transporters when compared to normal levels at an early point of PD. This may be predictive of how advanced the disease will be in five years. Generally, a pattern of reduced dopaminergic activity in the basal ganglia can aid in diagnosing PD.

One-sided Deficit in Parkinson's disease

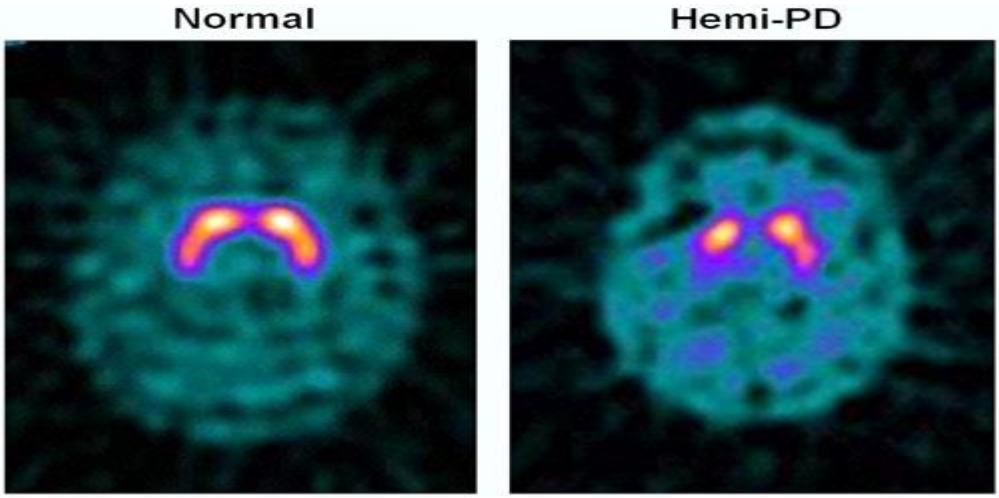

Figure No. 3: DaT Scan

Genetic Biomarkers

Genetic testing can identify a trait or susceptibility for Parkinson's disease but it is not used to determine the presence or progression of the disease. The presence of a certain gene does not definitively indicate that PD will develop. Genetic tests can be used to test for the presence of certain gene mutations but cannot be used to make a diagnosis of PD because the presence of the gene is not definitive. Recessive gene testing provides information but is not ideal for biomarker because the onset and progression of the disease is so slow.

Screening for biomarkers

Screening for biomarkers employs techniques that look for a pattern of variation in genes, protein, and small molecules using a biological sample such as saliva, blood, urine, or spinal fluid. The Michael J. Fox Foundation is using these techniques in an ongoing study of biomarkers called the Parkinson's Progression Markers Initiation (PPMI). They are looking at movement, cognitive, and brain biomarkers in addition to blood, urine, DNA, and spinal fluid sampling in 400 newly diagnosed PD patients over a 3-to-5-year period.

PATHOPHYSIOLOGY OF PARKINSON'S DISEASE

Although we are learning more each day about the pathophysiology of Parkinson's disease, it is still considered largely idiopathic (of unknown cause). It likely involves the interaction of host susceptibility and environmental factors. A small percentage of cases are genetically linked and genetic factors are being intensely studied.

Physiologically, the symptoms associated with Parkinson's disease are the results of the loss of several neurotransmitters, most notably dopamine. Symptoms worsen over time as more and more of the cells affect by the disease are lost. The course of the disease is highly variable, with some patients exhibiting very few symptoms as they age and others whose symptoms progress rapidly.

Parkinson's is increasingly seen as a complex neurodegenerative disease with a sequence of progression. There is strong evidence that it first affects the dorsal motor nucleus of the vagus nerve and the olfactory bulbs and nucleus, then the locus coeruleus, and eventually the substantia nigra. The cortical area of the brain is affected at a later stage. Damage to these various neuronal

systems accounts for the multi-faceted pathophysiologic changes that cause impairments not just to the motor system but also to the cognitive and neuropsychological system (Kwan& Whitehill, 2011).

THE ROLE OF DOPAMINE

Dopamine, like other neurotransmitters, transmits chemical messages from one nerve cell to another across the synapse, a space between the presynaptic call and the postsynaptic receptor. Dopamine is secreted into the synapse from the membrane storage vesicle in the presynaptic membrane. It crosses the synapse and binds to the postsynaptic membrane, where it activates dopamine receptors. Unused dopamine remaining in the presynaptic cell, the excess dopamine is repackaged into storage vesicles and released once more into the synapse.

Within the synapse, as dopamine travels from one cell to another, it can be broken down and rendered inactive by two enzymes, MAO (monoamine oxidase) and COMT (catechol-O-methyl transferase). One therapeutic strategy introduces a MAO inhibitor into the synapse, which interrupts the action of the MAO enzyme and prevents the breakdown of dopamine. This allows more dopamine t remain in the synapse and increases the likelihood that it will bind to the postsynaptic membrane.

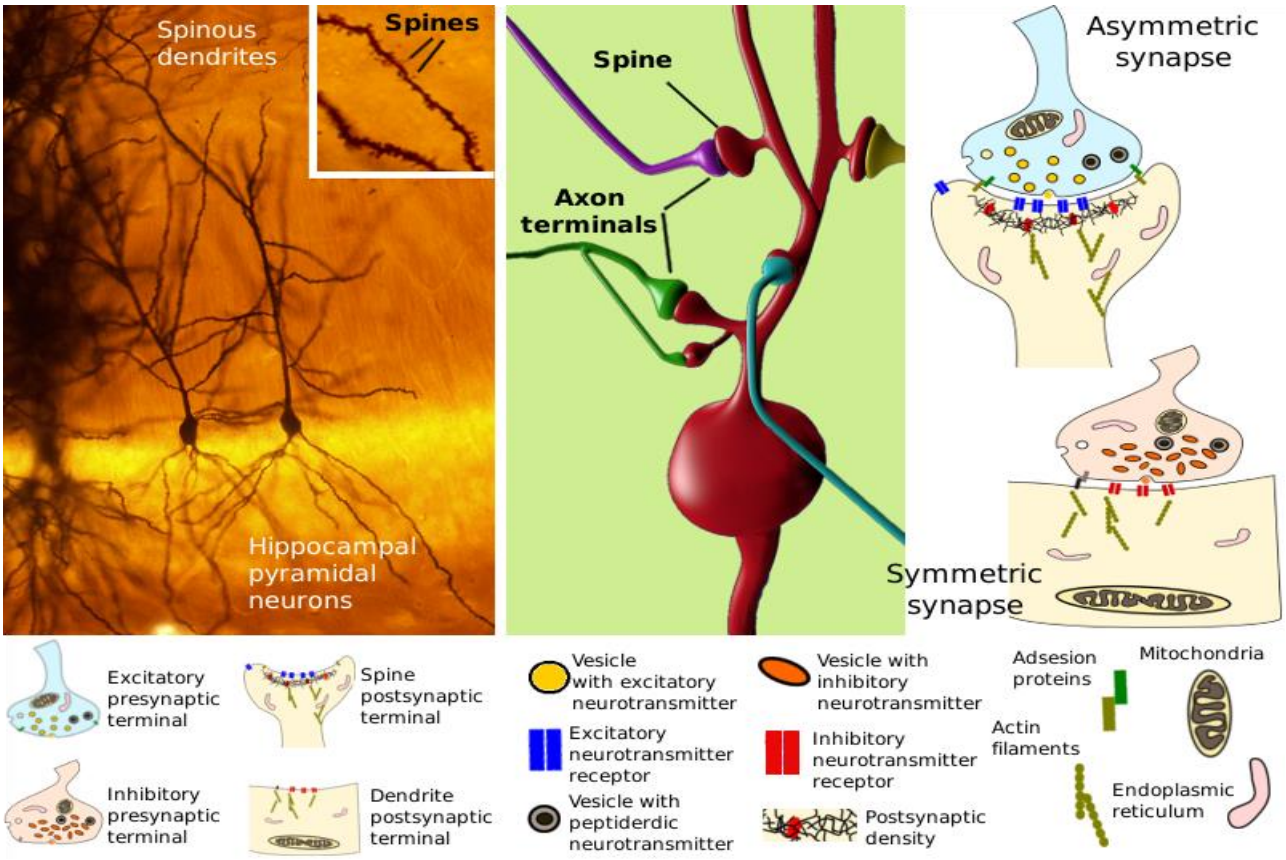

Figure No. 4: Role of Dopamine

An electrochemical wave called an action potential travels along the axon of a neuron, when the action potential reaches the presynaptic terminal, it provokes the release of a small number of neurotransmitter molecules, which bind to chemical receptor molecules located in the membrane of the postsynaptic neuron, on the opposite side of the synaptic cleft.

Progressive loss of dopamine

Although dopamine cell loss cannot be measured directly, measurements in neurologically normal people and in nonhuman primates reveal a slowly progressive loss of dopamine with age. In Parkinson's disease, the loss occurs at a much greater rate and both biochemical measures and imaging studies suggest there is a significant decrease in dopamine by the time motor symptoms appear. In this view, Parkinson's disease is an accelerated version of the cell death seen with normal aging (Cookson, 2009). This is illustrated in the graph below, which slows the decline of

dopaminergic neurons during normal aging, in idiopathic PD, in PD caused by environmental or genetic factors, and in early-onset.

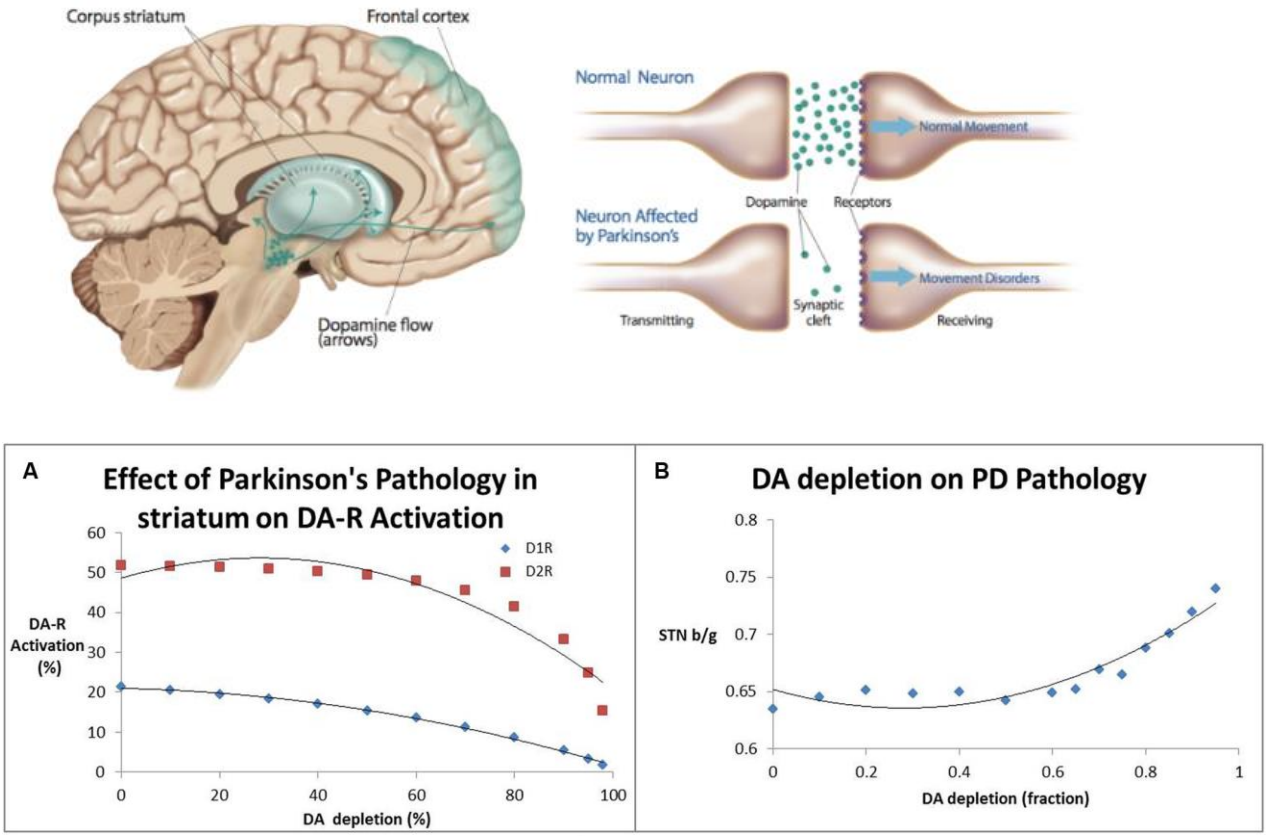

Figure No. 5: Progressive loss of dopamine

During normal aging (green line), small but slow dopaminergic degeneration occurs without any motor symptoms, idiopathic PD (IPD, blue line) is of unknown origin but is thought to develop gradually, with a slow degeneration of dopaminergic neurons leading to the classic PD motor symptoms later in life. Another model of dopamine neurodegeneration leading to PD motor symptoms involves repeated exposure to environmental toxicants over time in combination with a genetic predisposition to dopaminergic neuron loss (yellow line). Early-onset PD (red line), as caused by a mutation in the PARKIN gene, involves a precipitous decline in dopaminergic neurons, and PD motor can present decades prior to those in idiopathic PD. One more scenario (not shown) of PD motor symptoms development involves possible in utero environment toxicants or genetic factors leading to an atypically low number of dopaminergic neurons at birth and increased susceptibility to PD development.

Degeneration of dopamine neurons is particularly evident in a part of the substantia nigra called the pars compacta to increase the overall excitatory drive in the basal ganglia, disrupting voluntary motor control and causing the characteristic symptoms of PD. Normalization of motor function is seen initially with levodopa treatment.

As the severity of PD increases, the depletion of dopamine leads to further changes in the basal ganglia pathways, including the altered function of other basal ganglia neurotransmitters such as glutamate, GABA, and serotonin. Although there is the relative vulnerability of dopamine-producing neurons in the substantia nigra, not all dopamine cells are affected in Parkinson's disease in some parts of the brain the dopamine-producing neurons are relatively spared.

Lewy bodies and alpha-synuclein Lewy bodies are abnormal aggregates and inclusion of protein that develop inside nerve cells in people with Parkinson's disease. The aggregations usually consist of insoluble fibrillary aggregates containing misfolded proteins. A large number of molecules have been identified in Lewy bodies but a protein called alpha-synuclein is the main component.

Lewy bodies (Alpha-Synuclein Inclusion)

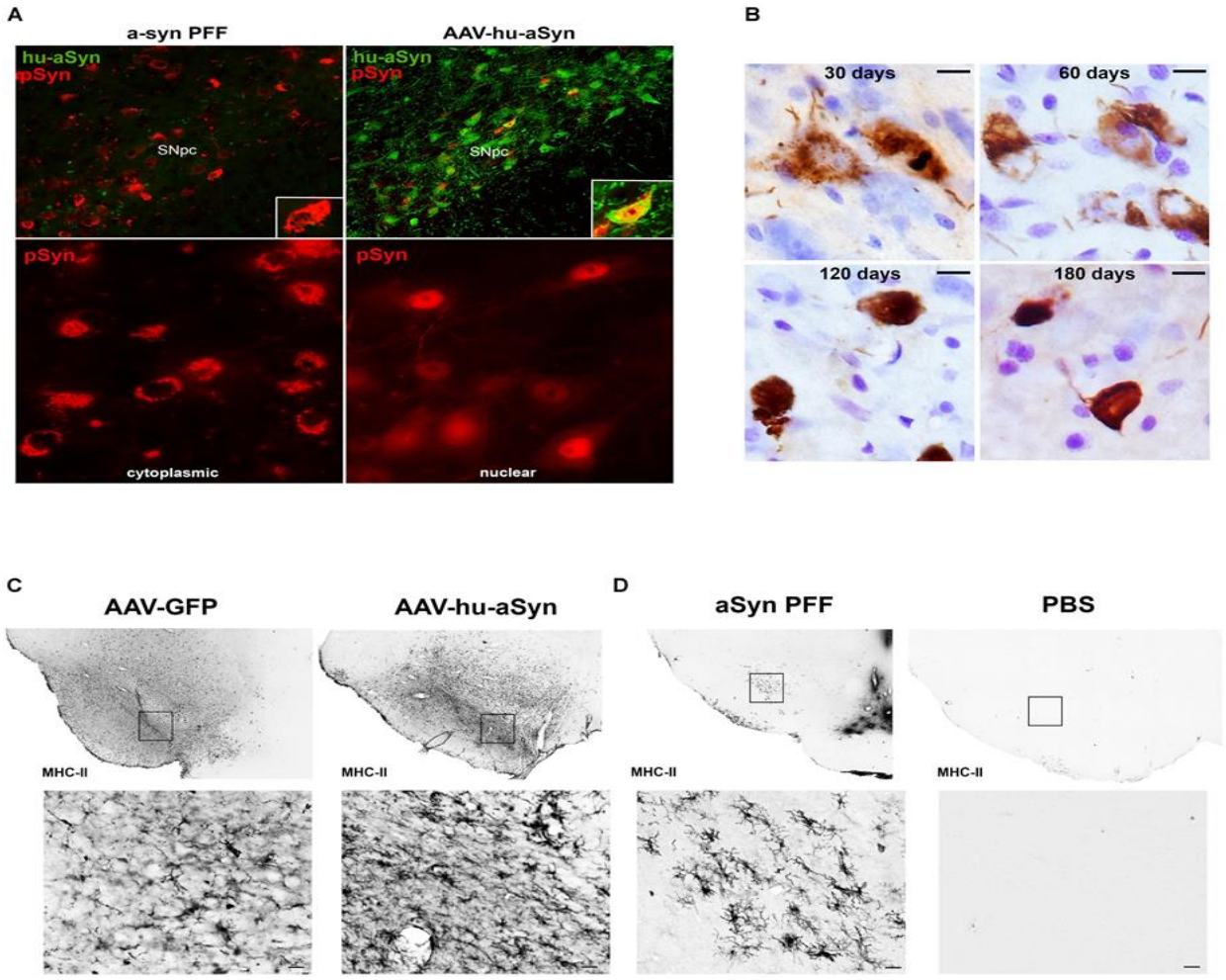

Figure No. 6: Lewy bodies (Alpha-Synuclein Inclusion)

Photomicrograph of regions of substantia nigra in a Parkinson's patient showing Lewy bodies and Lewy neurites in various magnifications, Top panels show a 60x magnification of the alpha-synuclein intraneuronal inclusion aggregated to from Lewy bodies. The bottom panels are 20x magnification images that show strand-like Lewy neurites and rounded Lewy bodies of various sizes.

Lewy pathology encompasses many regions of the brain and some reports have suggested that the substantia nigra is not the first place where Lewy bodies form in Parkinson's disease. Inclusion and aggregates likely symbolize the end stage of a cascade of complicated events. An

earlier stage may be more directly tied up to the pathogenesis of the disorder than the inclusion themselves, which may or may not represent a diagnostic hallmark.

Lewy bodies are also seen in "dementia with Lewy bodies," suggesting that these conditions are related to one another by shared pathology and possibly by shared etiology. Neither call loss nor the formation of Lewy bodies is absolutely specific for PD but both are required for a diagnosis of PD under the current definition.

Neurodegenerative disorders such as Alzheimer's disease, frontal temporal degeneration, prion disease, Huntington's chorea, and motor neuron disease are increasingly being realized to have common cellular and molecular mechanisms, including protein aggregation and inclusion body formation in certain areas of the nervous system.

Inflammation and Immune Response

The trigger of dopaminergic degeneration seems to be multifactorial affected by both endogenous and environmental elements. Inflammation and immune responses are increasingly being considered as important mediators of dopaminergic degeneration. Large population studies have suggested that individuals taking nonsteroidal anti-inflammatory drugs (NSAIDs) have less risk of developing idiopathic PD, which suggests that anti-inflammatory drugs may be the promising disease-modifying treatment for Parkinson's patients.

New trail phases have involved anti-inflammatory treatment specifically looking for an objective biomarker in treatments aimed at reducing inflammatory changes in patients with PD. Researchers are using neuroimaging tools to develop a relevant biomarker with the intention of testing this in large clinical imaging trials. The outcome of these trials will provide data to test and monitor the progression of anti-inflammatory treatment for PD and will help to identify the timely therapeutic window to stop, or at least slow, inflammatory-mediated dopaminergic degeneration.

Parkinsonism, also known as "atypical Parkinson's," "secondary Parkinson's," or "Parkinson's syndrome," is a neurological syndrome associated with Parkinson's disease- tremors, rigidity, bradykinesia, and postural instability. But Parkinsonism is not Parkinson's disease. Parkinsonism is nit though to be caused by Parkinson's disease and patients typically respond poorly to

pharmacological intervention, Parkinsonism often has an identifiable cause, such as exposure to toxins, methamphetamine, trauma, multiple strokes, other nervous system disorders, or illness. Generally, Lewy bodies are not seen in Parkinsonism's.

The term parkinsonism is also associated with disorders such as progressive supranuclear palsy, multiple system atrophy, Lewy body dementia, corticobasal degeneration vascular Parkinsonism, drug-induced Parkinsonism, and Parkinsonism secondary to infection and other causes. A form of reversible Parkinsonism can occur from the use of certain neuroleptic drugs, particularly reserpine, antipsychotic (haloperidol), and metoclopramide. Exposure to certain toxins, severe carbon monoxide poisoning, and mercury poisoning can also lead to Parkinsonism.

The appearance in the early 1980's of Parkinsonism symptoms in a group of drug addicts who had consumed a contaminated batch of a synthetic opiate led to the discovery of the chemical MPTP as an agent that causes Parkinsonism syndrome in nonhuman primates as well as in humans. MPTP can be produced when making a form of heroin (MPTP is converted to a neurotoxin that selectively destroys dopamine cells in the substantia nigra). These cases are rare and have mostly affected long-term drug users.

Methamphetamine abuse has also been linked to Parkinsonism. In experimental animals, exposure to methamphetamine damages dopaminergic fibers in the striatum as well as the call bodies in the substantia nigra, echoing the degeneration observed I human patients with PD. Selective damage to dopaminergic terminals in the striatum has also been observed in human methamphetamine users, although there is no evidence so far that methamphetamine abuse dopaminergic call bodies in the substantia nigra.

It has been hypothesized that methamphetamine use may predispose users to the future development of PD. This hypothesis has been supported by recent epidemiologic work indicating that methamphetamine users have an increased risk of developing PD. This is consistent with the persistent neurotoxin effects of methamphetamine in experimental animals.

Patients with Parkinsonism are often difficult to manage as outpatients. The complexity of their symptoms, the added cognitive and autonomic deficits, the poor response to most PD medications, and the relatively rapid decline in status contribute to the challenges in managing these patients, particularly as the disease progresses.

MEDICAL MANAGEMENT OF PARKINSON'S DISEASE

Because diagnosis is based on medical history, neurologic examination, and observation over time, a correct diagnosis is critical for effective management of the disease. Since many other diseases have similar features (especially when symptoms are mild), a timely and precise diagnosis is important so that patients can receive the proper and early treatment.

Brain scans and laboratory tests that can identify the presence of PD in vivo, Parkinson's can currently only be definitively confirmed through its pathological hallmark of Lewy bodies and Lewy neurites upon postmortem analysis. In the absence of confirming tests, the patient's response to levodopa is often used to confirm the presence of PD.

There is a consensus among clinicians and researchers that new medical treatments for Parkinson's disease should move from treating symptoms to modifying the disease pathology. The ultimate goal is to find a neuroprotective treatment that stop or even prevents neurological degeneration.

Symptomatic Treatment

Symptomatic Parkinson's disease therapies are designed to alleviate motor and nonmotor symptoms, delay the progression of the disease, and manage the side effects of treatment. The challenges faced by clinicians are to find the best treatment for each patient, re-evaluating as symptoms change. Among the many symptoms that occur in PD, cognitive changes, fatigue, anxiety and depression, sleep disturbances, and bladder and bowel dysfunction are usually treated successfully with a variety of drugs.

Early PD symptoms can be vague- increased clumsiness with the hands, mild gait irregularities, and intermittent tremor that is most obvious when the hand is resting or suspended when walking. Tremor, when present, is regular and rhythmic. Several nonmotor symptoms such as loss of smell, sleep disturbance, sensory changes, and pain can occur well before motor symptoms are evident.

Dopamine Replacement

The pharmacological mainstay for the treatment of Parkinson's disease is the replacement of dopamine with levodopa, a precursor of dopamine. Dopamine replacement poses many challenges because only 10% of a levodopa dose actually crosses the blood-brain barrier and enters the brain. The remaining levodopa is susceptible to conversion to dopamine in the periphery, leading to side effects such as nausea, dyskinesias, and joint stiffness. To address this, inhibitors that reduce the breakdown of dopamine in the peripheral nervous system called peripheral dopa decarboxylase inhibitors are given in combination with levodopa to reduce peripheral conversion that would otherwise devour most of the dose given. The addition of dopa decarboxylase inhibitors also maximizes the bioavailability of dopamine in the brain, decreases side effects, and allows a lower dose of levodopa to be used.

Once in the brain, as dopamine travels from one cell to another, it can be broken and rendered inactive by two enzymes, MAO (monoamine oxidase) and COMT (catechol-O-methyl transferase). One therapeutic strategy introduces a MAO inhibitor into the synapse, which interrupts the action of the MAO enzyme and prevents the breakdown of dopamine in the synapse. This allows more dopamine to remain in the synapse and increases the likelihood that it will bind to the postsynaptic membrane.

Although levodopa helps in at least three-quarters of Parkinsonian cases, not all symptoms respond equally to the drug. Bradykinesia and rigidity respond best, while tremor may be only marginally reduced. Problems with balance and other symptoms may not be alleviated at all. The controlled release version of levodopa in the form of intravenous and intestinal gel infusion spread out the medication and are showing promise.

Initial drug treatment may start with MAO-B inhibitors and dopamine agonists. Levodopa plus a dopa decarboxylase inhibitor (such as carbidopa) are used sparingly at first to delay as long as possible the side effects resulting from cumulative exposure of systemic dopaminergic function.

As the disease progresses and dopaminergic neurons continue to lose in the substantia nigra, L-dopa eventually becomes ineffective for treating the motor symptoms and may concurrently cause dyskinesia. As medication becomes less effective, "off" period may occur when the levodopa dose has worn off and movement is again difficult until a new dose is given.

Medication to treat nonmovement-related symptoms of PD, such as sleep disturbances and emotional problems, is also considered as needed.

After prolonged therapy with levodopa, a person with PD may alternate between phases with a good response to medication and few symptoms (the "on" stage) and phases (the "off" stage). Levodopa doses are therefore kept as low as possible, after using an alternative such as dopamine agonists and MAO-B inhibitors. Most people with PD will eventually require levodopa and hence later develop motor side effects such as involuntary movements, painful leg cramps, and a shortened response to each dose.

Transdermal Patches and Intestinal Gels

Transdermal dopaminergic patches are a recently developed therapy that has important advantages over pills and injections medications. A patch formulation provides a more constant drug delivery, offers the possibility of a once-a-day alternative. Additionally, pills may lose some clinical effectiveness when they are processed in the liver. The idea of a patch for a disease such as PD, where they are multiple drugs and multiple doses, is therefore very attractive to patients and caregivers.

Duodopa is a new therapy recently out of clinical trials in the United States. Duodopa was approved for use in Europe in 2004. It may provide significant benefits by improving "on" time and reducing on-off fluctuations and patient to wear a large external "box" in the belt region that is used to administer the intestinal gel preparation through a surgically placed intestinal tube.

Duodopa requires an attentive caregiver who must manage the device, the skin surrounding the tube, and medication refills. Early studies have revealed high rates of device-related problems with the intestinal tube (such as clogging, kinking, and moving out of the correct location). Despite these tube-related issues, Duodopa will likely be a great choice for many patients with on-off fluctuations, and will in most cases allow discontinuation of oral PD drugs.

Dopamine Agonists

Dopamine agonists are molecules that bind to the postsynaptic dopamine receptors and mimic the role of dopamine in the brain, causing a response similar to dopamine itself. Agonists were initially used to alleviate symptoms during the "off" state in patients with late PD when the

benefits of levodopa doses were wearing off. Agonists are also used as an early alternative to levodopa so that complications and dyskinesias are postponed for as long as possible.

Table No. 1: Dopamine Agonists

Generic Name	Brand Name
Bromocriptine	Parlodel, cycloset
Pramipexole	Mirapex
Ropinirole	Requip
Piribedil	Pronoran, Trivastal retard, Trastal, trivastan
Cabergoline	Dostinex, Cabaser
Apomorphine	Apokyn, Ixense, Spontane, Uprima
Lisuride	Dopergin, Proclacal, Revanil

Dopamine agonists produce significant, though usually mild, side effects such as drowsiness, hallucinations, insomnia, nausea, and constipation. Agonists have also been related to impulse control disorders such as compulsion sexual activity, compulsive eating, and pathologic gambling and shopping. If side effects appear even at a minimally effective dose, another drug from this class can be tried as an alternative. These drugs are less effective than levodopa in the control of motor symptoms but are usually sufficient in the earliest stages of the disease.

Apomorphine may be used to reduce "off" period and dyskinesia in late PD, though it requires injections or continuous subcutaneous infusion and may cause confusion and hallucinations. Apomorphine treatment obviously requires close attention from caregivers. Two other dopamine agonists are available as skin patches and have benefit I early stages and for the "off" state in advanced stages of PD.

MAO-B inhibitors

Selegiline (Eldepryl, Deprenyl, or Selgene) and rasagiline (Azilect) are MAO-B inhibitors that increase the level of dopamine in basal ganglia synapses by (MAO-B) enzyme responsible for breaking down dopamine. Like dopamine agonists, MAO-B inhibitor alone ca improve motor symptoms and delay the need for levodopa early in the disease, but they are less effective than

levodopa. In advanced diseases, they can be used to reduce fluctuations between “on” and “off” periods. None of these treatments slows the progression of the disease.

Other PD Treatment

Amantadine (Symmetrel) is a weak antagonist of NMDA-type glutamate receptors that increase dopamine release and blocks dopamine re-uptake in the synapse. It can be taken with levodopa to treat motor response fluctuations in advanced disease.

Anticholinergics that block the neurotransmitter acetylcholine in the central and peripheral nervous system may be useful to treat motor symptoms by essential anesthetizing the muscle-nerve connections to reduce unwanted motor symptoms and rigidity.

Several drugs have been used to treat other symptoms common to PD patients, such as the use of clozapine (Clozaril, FazaClo) for psychosis, cholinesterase inhibitors for dementia, and modafinil for daytime sleepiness. Some studies have implied that regular users of non-steroidal anti-inflammatory drugs (NSAIDs, apart from acetaminophen and aspirin), have a lower risk of ever developing PD. Other medications are listed in the following table.

Table No. 2: Other PD Treatment

Drug	Purpose
Memantine (Namenda), Rivastigmine (Exeleon), Galantamine (Razadyne)	Treatment of cognitive difficulties- these are NMDA receptor antagonists or acetylcholinesterase inhibitors.
Antidepressants	Treatment of mood disorders
Gabapentin (Neurontin, Gralise, Fanatrex)	Treatment of certain types of seizures or restless legs syndrome
Duloxetine (Cymbalta)	Treatment of depression, anxiety, peripheral neuropathy, fibromyalgia, or chronic pain related to muscles and bones. This is a selective serotonin and norepinephrine reuptake inhibitor.
Fludrocortisone, Midodrine, Botox, sildenafil	Treatment of autonomic dysfunction
Armodafinil (Nuvigil), Clonazepam (Klonopin), Zolpidem (Ambien)	Treatment of sleep disorders and daytime wakefulness

Treatment of L-dopa Induced Dyskinesia Levodopa remains the most effective agent to improve motor symptoms in PD but, as noted earlier, chronic use is associated with the emergence of motor fluctuations. This is manifested by a loss of clinical benefit before the next levodopa dose (wearing off)), dyskinesia (abnormal involuntary movements), and nonmotor complications, such as behavioral and cognitive changes.

In most patients' L-dopa treatment begins with a "honeymoon" period during which motor symptoms are well controlled. However, after 5 years of treatment, approximately 40% of patients develop fluctuations in symptom control in response to the drug, as well as involuntary movements are known as "L-dopa- induced dyskinesia" (LID). These complications affect as many as 89% of PD patients after 10 years of L-dopa treatment.

Dyskinesia usually improves when dopaminergic therapy is reduced but the reduction often causes PD symptoms to worsen. As the "off" state gets longer, bradykinesia usually increases, motor performance worsens, and daily activities are adversely affected.

Three risk factors are associated with increased occurrence of dyskinesia younger age at disease onset, longer disease duration, and longer duration of dopaminergic treatment. The first two factors are interrelated and almost all patients with early-onset Pd develop dyskinesias, whereas they are less frequent in patients with late-onset PD. Other risk factors associated with increased risk of dyskinesias are female gender and the occurrence of specific polymorphisms for dopamine receptors or dopamine transporters.

Peak Dose Dyskinesia Dyskinesias more commonly appear as choreiform, but in some cases, they may resemble dystonia, myoclonus, or other movement disorders. Peak dose dyskinesias are the most common type of dyskinesia, which occurs during peaks of levodopa-derived dopamine I the brain when the patient is otherwise experiencing a beneficial response. Peak dose dyskinesias worsen with an increase in dopaminergic dose and lessen when dopamine is reduced.

Diphasic Dyskinesia

In certain cases, dyskinesias appear with an alternative pattern (dyskinesia-improvement-dyskinesia). This is termed diphasic dyskinesia, and it tends to occur when levodopa-derived dopamine concentrations are increasing or decreasing. Diphasic dyskinesias are typically

displayed with large-amplitude stereotypic, rhythmic, and repetitive movements, more often of the legs, that may be associated with parkinsonian features in other body regions. In extreme cases, patients treated with levodopa can cycle between "on" period, which is complicated by disabling dyskinesia, and "off" periods, in which Parkinsonism is uncontrolled and the patient is akinetic and frozen.

Motor complications occur in about 50% of patients with PD who have been in therapy with levodopa for more than 5 years, and in almost 100% of patients with the young-onset disease. Achieving an acceptable clinical control once these motor fluctuations have appeared is usually a relatively simple matter, increasing the frequency of the levodopa doses or adding a medication that reduces "off" time. However, when a patient develops peak dose dyskinesias too, it becomes difficult to smooth the clinical response. Although for many patient's dyskinesia are not disabling, they create a barrier to adequate treatment of fluctuations and Parkinsonian symptoms.

Deep Brain Stimulation

Deep brain stimulation (DBS) was approved by the FDA in 1997. It is recommended for people who have PD and suffer from motor fluctuations tremors inadequately controlled by medication, or for those who are intolerant to medication, as long as they do not have severer neuropsychiatric problems. About 85,500 people worldwide have had DBS.

Deep brain stimulation is a surgical intervention that utilizes an implantable DBS lead. Each DBS lead has multiple contacts and therefore many possible parameter configurations. The optimization of possible settings, which may number into the thousand when considering the range of pulse widths, frequencies, amplitudes, and cathodes can, provides a critical determinant for therapeutic success or failure.

Deep brain stimulation is a two-stage procedure involving a stereotactic frame, with the patient under sedation yet awake, for a 30-minute, three-dimensional MRI to locate the coordinates of the deep brain target. The DBS electrode is placed, and electrical impulses are sent to see which placement gives the best reduction in tremors while monitoring for other unwanted side effects in speech or numbness.

Once an effective place is found, the electrode is left in and clipped into place on the skull, and the exterior wound is closed. A second operation is performed under general anesthetic to place a small battery pouch containing the stimulator pulse generator under the collarbone. From there, a wire is passed under the skin up the neck to behind the ear, where it re-emerges and is attached to the stimulator wire in the brain. After observation of several weeks, the unit will be turned on and tested further. Depending on the targeted region of the brain, a neurologist will be involved with the delicate electrode placement, and one or both sides of the brain may be targeted, in a similar but separate operation.

Determining Candidates for DBS

In deciding candidates for DBS, a good carbidopa/levodopa (Sinamet) profile is considered a key determinant for success. A person with a good Sinamet profile:

▫ Shows dramatic improvement in response to Sinamet

▫ Experiences a dramatic difference between “on” and “off” states

▫ Appears near normal in the “on” state

▫ Spends most of the day “off”

Deep brain stimulation has shown good results with certain symptoms of PD while having little effect on other common symptoms. Dyskinesias and tremors are the symptoms most commonly helped. DBS can reduce on/off fluctuation (more “on” and less “off”) and can also address:

▫ Dyskinesias

▫ Tremor

▫ Stiffness

▫ Slowness of movement, including freezing episodes

▫ Shuffling gait

Deep brain stimulation does not help:

▫ Swallowing problems

▫ Softness of speech

▫ Constipation

▫ Drooling

▫ Memory difficulties

Complications in Deep Brain Stimulation

Deep brain stimulation is associated with certain complications. Because an electrode penetrates the brain, there is a slight risk of puncturing small or medium-sized blood vessels. This occurs in 2% to 3% of cases, although permanent brain damage occurs in only 0.6% of cases or 1 in 200. Infections occur in 4% to 5% of cases and may require removal of the hardware, although the brain electrodes are usually left in place. The most common site of infection is in the chest where the battery pack is located.

In less than 2% of cases, DBS has no effect, and symptoms fail to improve, either due to malpositioned electrodes or because of an incorrect diagnosis. The success of DBS depends on a confident diagnosis and the choice of a good candidate. “Garden variety” PD responds well to DBS.

If other movement disorders that mimic PD are present, DBS is not effective. Red flags for the presence of something other than PD include more brain atrophy on MRI than is expected for a person’s age, evidence of severe vascular disease, or signs of another neurologic disease. A clinician should be suspicious of other neurologic disorders if these factors are present:

▫ Rapid onset of symptoms

▫ Rapid progression of symptoms

▫ Early onset of symptoms (early memory loss)

▫ Postural instability soon after diagnosis

▫ Autonomic failure soon after diagnosis

▫ Unusual finding on exam or MRI

Sinamet responsiveness is often used to determine the presence of PD, and a trial of this medication should improve symptoms. Tests are performed before and after medication, and a 30% improvement after talking Sinamet is considered a good response and usually correlated with a good response to DBS. Deep brain stimulation generally does not make symptoms better than a person's best "on" state; rather< it tends to make "off" period more like the "on" period.

Degree of disability is important when considering DBS. Generally, it is not recommended I the early stages of PD when a patient is doing well on a consistent amount of medication that is controlling symptoms throughout the day. These patients are encouraged to wait, partly because the technology is improving rapidly. At the other end of the spectrum, patients should not wait until symptoms have progressed so far that medications are ineffective.

Impaired Memory and Cognitive Function

Parkinson's patients with impaired cognition generally do not do well with DBS, partly because the procedure is complicated and the patient must be able to reliable and clearly explain symptoms. Specific memory testing is now done on all patients to try to identify cognitive issues. If DBS is done in someone with memory problems, it is usually done on one side of the brain, and patient is allowed to fully recover before the second implant is considered.

Age is also a consideration with DBS, although there is no cut-off age. Of concern is that with age the benefits associated with DBS decrease and the risk increases. Those over the age of 75 see only modest benefit and patients over the age of 80 are rarely offered DBS.

Some other medical problems increase the risk of a poor outcome with DBS. Poorly controlled hypotension can make blood pressure difficult t control during surgery. Significant cardiac disease increases risk, especially in patients on blood thinners, which must be stopped a week before DBS surgery and remain stooped for a week after surgery. Other medical conditions such as diabetes or the use of steroid medications increase the risk of infection: this does not contraindication the DBS in many cases.

Long-Term Results Following DBS

Long-term results depend on which region of the brain receives DBS. Stimulation of certain areas of the brain primarily reduces limb tremor. Targeting either areas appear to reduce all of the major motor problems with PD, including those dyskinesias that arise after extended use of levodopa.

While the effects of DBS are not more effective than a dose of levodopa, it does seem to reduce the time spent in the "off" states and it allows a reduction in levodopa use so that side effects further into the future.

A study in Italy, which followed 14 patients for several years after DBS surgery, showed a 56% improvement after 1 year, a 45% improvement after 5 years, and 42% improvement after 9+ years. The symptoms varied, however; tremors had the best-sustained improvement, gait improved significantly after 1 year but declined over the next 8 years. Posture, balance, and ADLs 9eg, rising from a chair) improved significantly after 1 year with no further improvement after 9 years.

Pallidotomy

Pallidotomy is a procedure in which a tiny electrical probe is placed in the globus pallidus (part of the basal ganglia), which is then heated to 80℃ 60 seconds, to ablate a small area of brain cells. Pallidotomy is an alternative to DBS for the treatment of levodopa-induced dyskinesia, and it can be an alternative to DBS for treating difficult cases of essential tremors.

Stem Cell Therapies

Stem cells are undifferentiated cells without mature, tissue-specific characteristics that are able to reproduce themselves by division into identical daughter cells. In response to proper stimuli, stem cells can produce more specific progenitor cell that can further differentiate into one or more functional call types. Stem calls represent a very promising source of call replacement therapy in several diseases, including PD, due to these key properties, namely, self-renewal and multipotential as well as the possibility to manipulate these cells in vitro.

Dopaminergic neurons can be generated from stem cells of different source. Embryonic stem cells (ESCs) have unlimited self-renewal capacity and are pluripotent since they are able to generate call of all three germ layers. Somatic (tissue-derived) stem cells can be isolated from developing tissues of the fetus or in the newborn, juvenile, or adult organism. Somatic stem cells have a more limited proliferation capacity than ESCs and are termed multipotent, typically being able to differentiate into the different cell types of one germ layer. Potential group of stem cells of PD call therapy include embryonic stem cells, neural stem calls, mesenchymal stem calls, and more recently, induced pluripotent stem call.

The most important question regarding using stem cells as a therapy for PD remains whether it is possible to generate a large number of cells with the capacity to survive and function as dopaminergic neurons following transplantation; also, to ensure that these cell-derived grafts do not show adverse effects such as tumor formation or immune rejection.

Types of Stem Cells

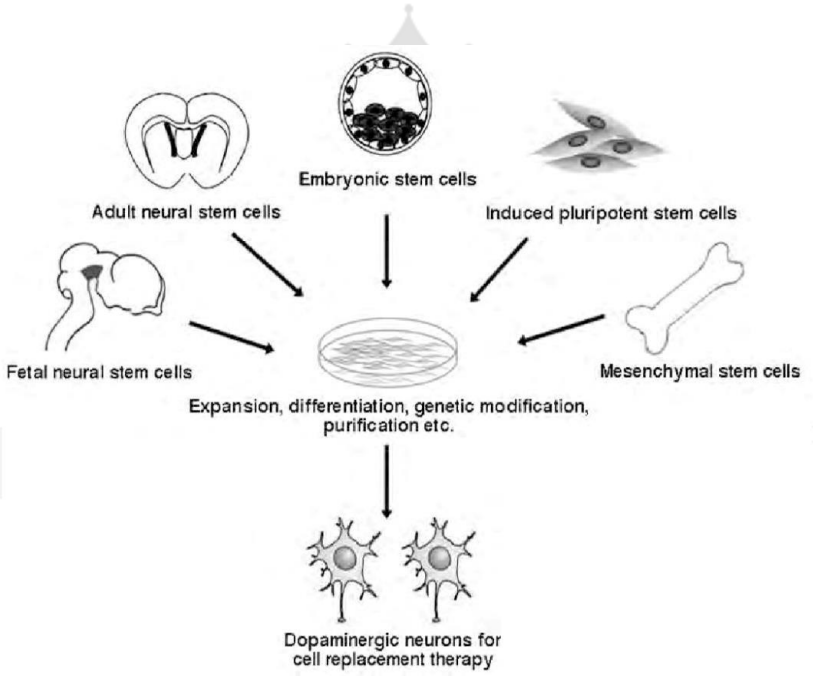

Figure No. 7: Types of Stem Cells

Since the 1980's fetal porcine carotid body cells or immature retinal tissues have been used in cell transplants, in which dissociated cells are injected into the substantia nigra in hope that they incorporate themselves into the brain and replace the dopamine-producing cells that have been

lost. Though the results of dopamine-producing cells transplants were initially positive, further trials have not shown benefits beyond other types of current therapy. In some cases, the new cells were secreting more dopamine then was necessary, leading to the dystonia common in advanced PD.

Stem cell transplants continue to be a research target because stem cells are easy to grow and manipulate, and when transplanted into the brain of rodents and monkeys they have been able to survive and reduce abnormalities. Reprogramming of cells using pluripotent stem cells derived from the patient is being actively studied.

Several molecules have been proposed as potential treatments aimed at reducing the rate of degeneration in PD patients. None of them have been convincingly shown to reduce degeneration.

Inhaled Levodopa

Clinical trials, partly funded by the Michael J. fox foundation, are underway on an inhaled formulation of levodopa. Called CVT-301, the therapy is designed to function as a sort of "rescue drug" to be taken in conjunction with the traditional pill form of levodopa/carbidopa (Sinemet). The idea is that patients taking CVT-301 could self-medicate by taking a puff from an inhaler should they feel an "off" period coming on. The medication is inhaled into the lungs and passes into the bloodstream much more quickly than oral medication.

In December 2018, the U.S. Food and Drug Administration (FDA) approved Inbrija (levodopa inhalation powder) for the intermittent treatment of "off" episodes in people with Parkinson's disease who are already treated with carbidopa/ levodopa. Inbrija, an inhaled version of levodopa, provides a new method of delivery for this medication.

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19. midbrain of affected and normal person

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