



IJPPR

INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals

ISSN 2349-7203



Human Journals

Review Article

June 2022 Vol.:24, Issue:3

© All rights are reserved by Vanita G. Kanse et al.

A Review of Diagnostic Techniques for Parkinson's Disease

			
Vanita G. Kanse*¹, Megh M. Thosar²			
<i>1 HOD, Department of Pharmacology, Oriental College of Pharmacy, Sector 2, Behind Sanpada Railway Station, Sanpada West, Navi Mumbai-400705, Maharashtra, India.</i>			
<i>2 Department of Pharmacology, Oriental College of Pharmacy, Sector 2, Behind Sanpada Railway Station, Sanpada West, Navi Mumbai-400705, Maharashtra, India.</i>			
Submitted:	25 May 2022		
Accepted:	31 May 2022		
Published:	30 June 2022		

Keywords: Parkinson's disease, Lewy body, tremors, PET scan, substantial nigra

ABSTRACT

Parkinson's disease is the second most common progressive neurodegenerative disorder in older people. Idiopathic Parkinson's Disease is associated with risk factors such as aging, family history, pesticide exposure, and environmental chemicals (e.g., synthetic heroin use). It is caused by a pathophysiological loss or degeneration of dopaminergic neurons in the substantia nigra of the midbrain and the development of neuronal Lewy Bodies. Its underlying causes are unknown. Despite significant advances in neurodegenerative disease research since James Parkinson's first medical description of Parkinson's disease in 1817, these disorders continue to pose significant diagnostic and treatment challenges. A valid diagnosis at early disease stages is critical because it can help accommodate differential prognostic and disease management approaches, elucidate reliable clinicopathological relationships ideally at prodromal stages, and would make it easier to evaluate innovative treatments in clinical trials. The pursuit of early diagnosis in Parkinson's disease and atypical Parkinsonian syndromes, however, is hampered by significant clinical and pathological heterogeneity, which can affect disease presentation and progression. Therefore, more accurate more specific diagnostic techniques are required to differentiate Parkinson's disease from other neurological conditions.



www.ijppr.humanjournals.com

INTRODUCTION:

Parkinsonism, which is defined by the presence of cardinal clinical motor features such as rigidity, bradykinesia, and tremor, has an impact on patients' ability to function and can lead to a significant loss of quality of life. Parkinson's disease (PD) is the most common cause of neurodegenerative Parkinsonism, affecting over 10 million people worldwide and imposing a significant socioeconomic burden. (1) The motor symptoms of Parkinson's disease, particularly in the early stages, are largely caused by the loss of dopamine-producing neurons in the substantia nigra pars compacta (SNpc), whereas non-motor features such as olfactory and autonomic dysfunction, sleep disorders, psychiatric symptoms, depression, pain, fatigue, and cognitive impairment are caused by more widespread neurodegeneration involving other neurotransmitter systems(2)(3). PD patients often respond well to levodopa based on dopaminergic denervation. Atypical Parkinsonian syndromes (PS) are a set of heterogeneous neurodegenerative diseases that also show with Parkinsonism, but they generally do not react well to levodopa treatment and are treated as separate clinicopathological disorders.

Dopamine (DA) is a neurotransmitter that has numerous functions in the brain and body (4). Dopamine acts as a neurotransmitter in the brain, which is a substance secreted by neurons (nerve cells) to relay signals to other nerve cells. Neurotransmitters are generated in specific areas of the brain, yet they have a wide-ranging effect. There are multiple unique dopamine pathways in the brain, one of which is important in the motivational component of reward-motivated behavior (5). Other dopamine pathways in the brain participate in motor control and the release of numerous hormones. These routes and cell types combine to generate a neuromodulatory dopamine system.

The main pathological characteristic of PD is the cell death in the brain's basal ganglia. In Parkinson's disease, alpha-synuclein becomes misfolded and clumped together with other alpha-synuclein (6). Cells are unable to eliminate these aggregates, and alpha-synuclein becomes cytotoxic, causing cell damage. These clusters, known as Lewy bodies, can be detected in neurons under a microscope. In the substantia nigra, the loss of neurons is followed by the death of astrocytes (star-shaped glial cells) and a large increase in the number of microglia (another type of glial cell). Braak staging is a method of explaining the progression of the areas of the brain affected by Parkinson's disease (7). According to this staging, Parkinson's disease begins in the medulla and olfactory bulb before progressing to

the substantia nigra pars compacta and the rest of the midbrain/basal forebrain. When the disease begins to impact the substantia nigra pars compacta, movement symptoms appear.

Five major brain routes connect other brain locations to the basal ganglia. These routes are known as the motor, oculomotor, associative, and limbic (7). And orbitofrontal circuits, with the names denoting the circuit's primary projection area. All of them are affected in PD, so it explains many of the symptoms of the disease since these circuits are involved in a wide variety of functions, including movement, attention, and learning. The motor circuit has been studied the most in terms of science.

The major protein aggregates identified inside the brain, which are thought to be intimately engaged in the underlying pathogenic mechanisms, are used to classify neurodegenerative illnesses that cause Parkinsonism (8). Because of the presence of misfolded α -synuclein aggregates, Lewy body spectrum disorders (LBSD) such as Parkinson's disease (PD) with and without cognitive impairment, Parkinson's disease dementia (PDD), dementia with Lewy bodies (DLB), and multiple system atrophy (MSA) are classified as α -synucleinopathies. Tauopathies include progressive supranuclear palsy (PSP) and Corticobasal degeneration (CBD) due to the presence of aggregated tau inclusions in the brain (8). With greater knowledge of these disorders, the existence of "mixed" diseases is becoming more common.

According to research, Parkinson's disease is the result of a complex combination of genetic and environmental variables. Around 15% of individuals with PD have a first-degree relative who has the disease, and 5–10% of people with PD are known to have forms of the disease that are caused because of a mutation in one of several specific genes (15). Susceptibility variables put the individual at an elevated risk, typically in combination with other risk factors, which affect the age of onset, severity, and course of the disease. The development of PD has been linked to at least 11 autosomal dominant and 9 autosomal recessive gene mutations (9). A 22q11 deletion has also been linked to Parkinson's disease. Mutations in the LRP10 gene have been linked to an autosomal dominant type.

SNCA gene mutations are crucial in Parkinson's disease because the protein encoded by this gene, alpha-synuclein, is the major component of the Lewy bodies that collect in the brains of persons with Parkinson's disease (9). A key DNA damage-repair signaling kinase, ataxia telangiectasia mutated is activated by alpha-synuclein. Furthermore, alpha-synuclein stimulates the non-homologous end-joining DNA repair mechanism. The accumulation of

alpha-synuclein in Lewy bodies appears to represent a link between decreased DNA repair and brain cell death in Parkinson's disease (10).

Mutations in several genes, including SNCA, LRRK2, and GBA, have been identified as risk factors for "sporadic" (nonfamilial) Parkinson's disease. Mutations in the gene *LRRK2* are the most known cause of familial and sporadic PD, accounting for around 5% of individuals with a family history of the disease and 3% of sporadic cases. A mutation in GBA confers the highest genetic risk of acquiring Parkinson's disease (9).

Several Parkinson-related genes are involved in the operation of lysosomes, which are organelles that digest cellular waste. Some forms of Parkinson's disease may be caused by lysosomal diseases (9), which impair cells' capacity to break down alpha-synuclein.

SIGNS AND SYMPTOMS:

Tremor at rest, Rigidity, Akinesia (or bradykinesia), and Postural instability are the four cardinal symptoms of Parkinson's disease that can be grouped under the acronym TRAP. 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 form. Motor and nonmotor impairments should be assessed in the context of each patient's demands and aspirations, due to the various profiles and lifestyles of persons affected 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 difficulty in planning, starting, and executing movement as well as performing sequential and simultaneous tasks (11). Slowness in doing daily chores, as well as delayed movement and reaction times(12)(13), are common symptoms. This could include issues with tasks that require fine motor control (e.g., buttoning, using utensils). Loss of spontaneous motions and gestures, drooling due to impaired swallowing(14), monotone and hypophonic dysarthria, loss of facial expression (hypomimia) and decreased blinking, and diminished arm swing when walking are all manifestations of bradykinesia. It makes it difficult to do two separate motor activities at the same time, and it can be exacerbated by mental stress or concurrent illnesses. Surprisingly, persons with Parkinson's disease can often ride a bicycle or climb stairs more readily than they can walk on level ground. (15) Bradykinesia, like other parkinsonian symptoms, is

affected by the patient's emotional condition. Immobile patients, for example, who become excited may be able to perform fast movements such as catching a ball (or may be able to run if someone shouts "fire"). This phenomenon (kinesia paradoxa) shows that people with Parkinson's disease have intact motor programs but struggle to access them without an external trigger, such as a loud noise, marching music, or a visual indication forcing them to step over an obstacle. (16) Bradykinesia is thought to be caused by a disruption in normal motor cortex activity, which is mediated by diminished dopaminergic function. In a study of single cortical neuron recordings in rats with haloperidol-induced bradykinesia, a drop in firing rates was found to be associated with bradykinesia. (17) Functional neuroimaging studies also point to a problem with the recruitment of cortical and subcortical systems that control movement kinematics (e.g., velocity). (18)

Tremors:

The most typical presenting symptom is a coarse, slow tremor of the affected hand at rest, which fades with the voluntary movement of the affected arm and in deeper stages of sleep. It usually starts in one hand and spreads to the other as the condition progresses. The frequency of Parkinson's tremors ranges between 4 and 6 hertz (cycles per second). Rest tremor in Parkinson's disease patients can also affect the lips, chin, jaw, and legs, however, unlike essential tremor, it rarely affects the neck/head or voice. Thus, a patient with head tremor is more likely to have essential tremor, cervical dystonia, or both, rather than Parkinson's disease. (19) In addition to rest tremor, many people with Parkinson's disease also develop postural tremor, which is more noticeable and severe than rest tremor and maybe the disease's first symptom. The development of tremor in Parkinson's associated postural tremor ("re-emergent tremor") is often delayed until the patient assumes an outstretched horizontal stance, as opposed to an essential tremor. Because re-emergent tremor occurs at the same rate as classical rest tremor and responds to dopaminergic treatment, it is most likely a subtype of the more common rest tremor. (20)

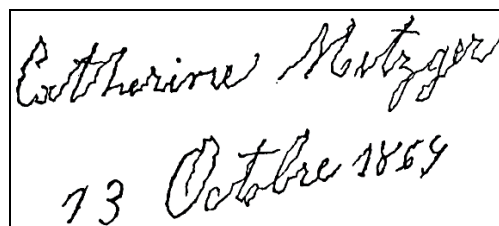


Fig.1 Handwriting of a PD patient

Rigidity:

Rigidity is defined by increased resistance, which is generally accompanied by the "cogwheel" phenomenon, especially when combined with an underlying tremor, and is evident across the range of passive movement of a limb (flexion, extension, or rotation of a joint). It can occur both proximally (neck, shoulders, hips) and distally (e.g., wrists, ankles). Rigidity is linked to discomfort, and a painful shoulder is one of the most prevalent early signs of Parkinson's disease, but it's often misdiagnosed as arthritis, bursitis, or rotator cuff damage (21).

Postural deformation:

Neck and trunk rigidity (axial rigidity) can arise, leading to aberrant axial postures (e.g., anterocollis, scoliosis). Rigidity is commonly accompanied by postural abnormalities that result in flexed neck and trunk posture, as well as flexed elbows and knees. Flexed posture, on the other hand, usually occurs later in the disease. Some patients may acquire striatal limb abnormalities (e.g., striatal hand, striatal toe). The striatal hand (Fig.1) is distinguished by ulnar deviation of the hands, flexion of the metacarpophalangeal joints, and extension and flexion of the proximal and distal interphalangeal joints; the striatal foot (Fig.2) is distinguished by toe extension or flexion (22). Patients with striatal abnormalities are typically younger and have an earlier start of parkinsonian symptoms (23). Some other skeletal deformations are extreme neck flexion ("dropped head" or "bent spine"), truncal flexion (camptocormia), and scoliosis (23-26).



Fig no.2 Striatal hand in a patient with PD



Fig no.3 Left side striatal toe

Posture instability:

Postural instability caused by a lack of postural reflexes is a late-stage PD symptom that usually appears after the start of other clinical characteristics. The pull test, which involves rapidly pulling the patient backward or forward by the shoulders, is used to determine the degree of retropulsion or propulsion. An aberrant postural reaction is defined as taking more than two steps backward or the absence of any postural response. Postural instability (combined with freezing of gait) is the most prevalent cause of falls and considerably increases the risk of hip fractures (27). The long time between the beginnings of falls distinguishes Parkinson's disease (PD) from other neurodegenerative disorders such as progressive supranuclear palsy (PSP) and multiple system atrophy (MSA). In one study, the average period from the onset of symptoms to the first fall in individuals with PD was 108 months, compared to 16.8 and 42 months in patients with PSP and MSA, respectively (27).

Freezing:

Freezing, also known as motor blocks, is a type of akinesia (lack of movement) and one of the most severe symptoms of Parkinson's disease (28). Although freezing is a common symptom of Parkinson's disease, it does not occur in all cases. According to one study, 47 percent of patients reported freezing; it happens more frequently in men than in women and less commonly in patients with tremors as their primary symptom (29). The legs are the most usually affected during walking, however, the arms and eyelids can also be affected (30). It usually manifests as a brief (about 10 seconds) incapacity to move. This can involve a hesitant start to walking or a sudden inability to move the feet in specific situations (e.g., turning or walking through a narrow passage, crossing busy streets, nearing a destination). Freezing has significant social and clinical effects on patients. It is a prevalent cause of falls, in particular (31). There are five varieties of freezing: start hesitation, turn hesitation, tight quarters hesitation, destination hesitation, and open space hesitation.

NON-MOTOR FEATURES:

Autonomic dysfunction:

Although autonomic failure is more commonly linked with MSA, it may be a presenting characteristic of PD. This includes orthostatic hypotension, sweating dysfunction, sphincter dysfunction, and erectile dysfunction (32) (33).

Neurobehavioral abnormalities:

Neuropsychiatric disorders can be equally incapacitating as motor symptoms. After 15 years of follow-up, the Sydney Multicentre Parkinson's Disease Study discovered that 84 percent of patients tested showed cognitive loss and 48 percent fulfilled the diagnostic criteria for dementia (34). Dementia caused by Parkinson's disease is frequently connected with several other neuropsychiatric disorders. Depression (58%) was the most commonly reported symptom among 537 such patients, followed by apathy (54%), anxiety (49%), and hallucinations (44%)(35). During an average of 14.6 months of follow-up, 27.6 percent of 114 Parkinson's disease patients tested positive for depression; 40 percent were neither treated with antidepressants nor referred for further psychiatric evaluation (36). In addition to cognitive and affective disorders, many patients with Parkinson's disease exhibit obsessive-compulsive and impulsive behaviors such as craving (especially for sweets)(37), binge eating, compulsive foraging, hypersexuality, pathological gambling, compulsive shopping, and punding, which is defined by an intense fascination with repetitive handling, examining, sorting, and arranging of objects(38). These behavioral symptoms, known as "hedonistic homeostatic dysregulation," have been linked to dopamine dysregulation syndrome, which is linked to the use of dopaminergic medicines, particularly dopamine agonists, although the mechanism underlying these abnormal behaviors remains unknown.

DIAGNOSIS:

The presence of the basic symptoms of slowness and paucity of movement (bradykinesia and akinesia) and tremors at rest or resistance to passive movement of the joints (rigidity), or both, is used to diagnose Parkinson's disease. Postural abnormalities are frequently included in the criteria, but they generally develop later in the disorder's progression and are vague, making them of little clinical utility in early disease (39) (40). Although a diagnosis of Parkinson's disease can be a simple clinical exercise in patients with typical presentations of cardinal signs and excellent response to levodopa treatment, differentiating the disease from other forms of Parkinsonism can be difficult, especially early in the disease when signs and symptoms of different forms of Parkinsonism overlap more.

DIFFERENTIAL DIAGNOSIS:

Essential tremor:

While diagnosing Parkinson's disease it is important to differentiate it from other forms of Parkinsonism such as progressive supranuclear palsy, multisystem atrophy, Corticobasal degeneration, essential tremor, etc. Essential tremor is a single-symptomatic condition characterized by the presence of apparent and persistent bilateral, typically symmetrical, postural, or kinetic tremors in the hands and forearms (41). Although bradykinesia, stiffness, and postural instability are not symptoms of essential tremors, still around 20% of people with essential tremors are misdiagnosed with Parkinson's disease and vice versa (42). The existence of head tremor, vocal tremor, and alcohol sensitivity significantly favors essential tremor. Because essential tremor is an autosomal dominant condition in many cases, a family history of a comparable tremor could also be informative. Classic rest tremor, primarily unilateral tremor, leg tremor, concurrent rigidity, and levodopa sensitivity all point to a diagnosis of Parkinson's disease.

Dementia with Lewy bodies:

After Alzheimer's disease, dementia with Lewy bodies is now considered the second most frequent type of degenerative dementia. Clinically, it is defined as a progressive dementia syndrome with substantial attentional and visuospatial impairments, marked instability in attention and cognition, visual hallucinations, and Parkinsonism, according to published consensus criteria. In addition to brainstem Lewy body disease, neuropathology reveals significant neocortical and limbic Lewy body degeneration (43). Neuropathologically, there is a more prominent temporal lobe Lewy body formation in dementia with Lewy bodies. Although this characteristic has been proposed to distinguish the two disorders based on the time of onset of dementia from the onset of Parkinsonism and to limit the term Parkinson's disease dementia to patients who develop dementia at least 12 months after the onset of the disease's motor manifestations (44).

Progressive supranuclear palsy:

Steel-Richardson-Olszewski syndrome, also known as progressive supranuclear palsy, is a multisystem degenerative disorder that can be easily distinguished from Parkinson's disease when a patient exhibits the typical clinical picture of supranuclear gaze palsy, which includes predominantly vertical gaze, parkinsonism, pseudobulbar palsy, and prominent frontal lobe

syndrome (45). Progressive supranuclear palsy can be misunderstood as Parkinson's disease in the early stages before gaze abnormalities appear, in patients without gaze palsy, or when full-blown Parkinsonism dominates the clinical symptoms. There are several diagnostic criteria for progressive supranuclear palsy that have been published. The most widely used for research are those developed by the National Institute of Neurological Disorders in the United States and the Society for Progressive Supranuclear Palsy (46). These criteria require that vertical supranuclear palsy and prominent postural instability with falls occur within the first year of disease onset for probable progressive supranuclear palsy.

Multisystem atrophy:

Multisystem atrophy is a sporadic multisystem degeneration characterized by α -synuclein deposits in the CNS (oligodendrocytic inclusions) but without Lewy bodies or neuritis. This disorder may present primarily or exclusively in cerebellar (olivoponto cerebellar atrophy) or parkinsonian (striatonigral degeneration) form. The parkinsonian variant of multisystem atrophy, known as MSA-p, can be difficult to distinguish from Parkinson's disease. Although MSA-p affects a slightly younger age group than Parkinson's disease, the peak of onset is still in the sixth decade. Only if prominent signs of autonomic failures, such as impotence or postural hypotension, appear early in the course of the disease, or if a clear cerebellar syndrome is present, can the disorder be reliably diagnosed. Other clinical features that can help distinguish MSA-p from Parkinson's disease include nocturnal stridor, rapid progression, early instability, and falls, stimulus-sensitive myoclonus, pyramidal tract signs, severe dysarthria, and insufficient or only transient response to levodopa(47).

GENETIC TESTING:

The number of genes involved with complex symptoms that include Parkinsonism and has been assigned PARK loci continue to grow, as does the list of mutations generating monogenic kinds of Parkinson's disease. Several other genes (such as GBA, GCH1, ADH1C, TBP, ATXN2, MAPT, and GLUD2) have been discovered as contributing factors to an elevated risk for the sporadic form of the disease, with heterozygous mutations in GBA being the most common and relevant(48). Genetic forms account for a small percentage of Parkinson's disease cases in clinical practice, and genetic testing is not currently part of the routine diagnostic process, except in patients with a strong suspicion of a genetic cause (for example, a suggestive family history, early onset (which is typical for several recessive genes), or specific clinical findings, such as dystonia as a presenting symptom). Overall, poor

penetrance and varied expressivity limit the consequences of genetic testing in clinical practice, and genetic findings have little impact on practical treatment decisions at this time. This may change in the future when data from prospective studies on the prognostic implications of genetic variants become available, and specific treatment targets in carriers of mutations linked to Parkinson's disease are being investigated(48). Currently, access to molecular genetic testing for the two most prevalent mutations (parkin [PARK2], and LRRK2 [PARK8]) is limited to research facilities, and the fees are prohibitively high.

CSF AND BLOOD TEST:

Although several studies have been conducted to compare the levels of various proteins, most notably the levels of different alpha-synuclein species, in the cerebrospinal fluid (CSF) of patients with Parkinson's disease versus controls, the sensitivities and specificities have been unsatisfactory, and currently, there is not a clinically useful CSF-based diagnostic test for Parkinson disease available (48). This is also true for blood biomarkers, even though correlations of several serum or plasma statistics with disease development have been observed, including correlations between lower plasma levels of apolipoprotein A1 and greater severity of motor symptoms.

One research group measured total alpha-synuclein. They created a new ELISA that uses a unique α -synuclein-specific antibody with good sensitivity and signal for quantifying α -synuclein in human plasma. Even though the study only included a small number of patients and control people, it is promising and could be used as a peripheral biomarker (49). Kinase(s) can phosphorylate alpha-synuclein at serine129 (PS129). The presence of highly phosphorylated α -synuclein in Lewy bodies indicates that it has a pathogenic role. Only 4% of phosphorylated alpha-synuclein is detected in healthy brains, whereas 90% is found in the brains of Parkinson's disease sufferers. Phosphorylated α -synuclein can cause damage to dopaminergic cells (6).

IMAGING:

In the early 1980s, the visualization of striatal dopamine depletion in Parkinson's disease patients using 18F-labeled L-dopa and PET was a milestone in molecular neuroimaging (50). Since then, the area of neuroimaging has made significant developments that are becoming increasingly relevant to Parkinson's disease (51). For example, ^{123}I -ioflupane single-photon emission CT (SPECT) (also known as DaTscan) is approved for clinical routine use and can

be utilized to distinguish Parkinson's disease from clinical mimics that do not have presynaptic nigrostriatal terminal failure (51). Structural MRI aids in the diagnosis of symptomatic Parkinsonism, and different MRI techniques can reveal particular alterations in the basal ganglia and infratentorial regions in atypical Parkinsonism. Diffusion-weighted imaging, volumetric imaging, automated subcortical volume segmentation, and multimodal imaging are among the advanced MRI techniques and post-processing procedures being investigated to improve diagnostic accuracy for Parkinson's disease versus other types of degenerative parkinsonism(52) (53).

<p>Panel 1: Routine MRI findings in degenerative Parkinsonism</p> <p>Parkinson's disease Substantia nigra signal void on high-field MRI</p> <p>Multisystem atrophy Infratentorial pathology Medullary and pontine atrophy Cerebellar and dentate atrophy Hyperintensity of middle cerebellar peduncle, cerebellum, inferior olives, pontine fibres (hot-cross bun sign) Dilated fourth ventricle Supratentorial pathology Putaminal atrophy and/or hypointensity Putaminal lateral hyperintensity (slit sign)</p> <p>Progressive supranuclear palsy Dilated 3rd ventricle Midbrain atrophy Globus pallidus hyperintensity Nucleus ruber hyperintensity Frontal cortical atrophy Temporal cortical atrophy</p> <p>Corticobasal degeneration Asymmetric parietal cortical atrophy</p>

SPECT (Single-photon emission computed tomography):

Source: Eduardo et al., 2006.(43)

The first SPECT tracer used for Parkinson's disease diagnosis was iodine-123 labelled 3-iodo-6-methoxybenzamide (IBZM). In the striatum, IBZM interacts to D2-dopamine receptors. Brücke and colleagues (54) were the first to show that in parkinsonian disorders with striatal pathology, striatal IBZM binding is lower than in Parkinson's disease. IBZM-SPECT revealed reduced D2-receptor binding in multisystem atrophy or progressive supranuclear palsy, which was later verified in a number of studies. The substantial overlap in postsynaptic D2-receptor binding between patients with Parkinson's disease and those with MSA or progressive supranuclear palsy limits the use of IBZM-SPECT to diagnose Parkinson's disease. In a comparison of diffusion-weighted MRI and IBZM-SPECT, diffusion-weighted MRI revealed more differentiation (55).

SPECT ligands for the presynaptic dopaminergic terminal have been approved for use in clinical trials. Tropane derivatives—CIT and FP-CIT (DaTSCAN)—bind to the DAT protein of nigrostriatal nerve terminals and are the most commonly employed tracers.

On 123I-FP-CIT SPECT, normal DAT binding appears as two brilliant symmetric "comma-shaped" areas, indicating high activity in the striatum (striatum includes caudate nucleus and putamen). On 123I-FP-CIT SPECT, any change in this activity could indicate presynaptic nigrostriatal damage (56). Diminished DAT binding on SPECT has been reported in patients with Parkinson's disease, DLB/PDD, MSA, and PSP to variable degrees, indicating nigrostriatal degeneration. Several investigations have found an uneven reduction in striatal DAT binding using SPECT, even in the very early stages of illness. As a result, DAT-SPECT has been proposed as a sensitive early diagnostic marker for Parkinson's disease, with differential diagnostic potential for non-parkinsonian tremor diseases, drug-induced parkinsonism, psychogenic parkinsonism, and vascular parkinsonism(2).

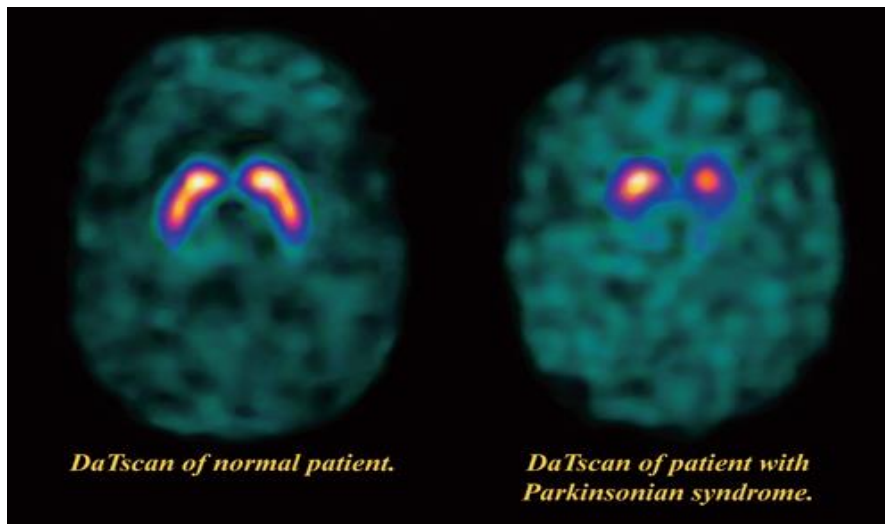


Fig no 4. DaT scan imaging

Another effective test for early differential diagnosis of parkinsonism is SPECT examination of sympathetic cardiac innervation with iodine-123 labeled meta-iodobenzylguanidine (MIBG). There has been a consistent reduction of tracer binding in patients with Parkinson's disease, showing postganglionic sympathetic cardiac denervation, in contrast to the discovery of retained MIBG cardiac binding in patients with multisystem atrophy or progressive supranuclear palsy. Overall, published studies show that cardiac MIBG-SPECT can distinguish Parkinson's disease from multisystem atrophy with greater than 90% sensitivity and specificity (43).

PET (Positron emission tomography):

Asymmetrically reduced putaminal absorption of the presynaptic dopaminergic PET ligand fluorine-18-labelled-dopa (18F-dopa) has been identified as a hallmark of Parkinson's disease. Cerebral glucose metabolism can be assessed using 18F-labeled fluorodeoxyglucose [18F-FDG], with lower tracer uptake indicating decreased tissue glucose use. On 18F-FDG-PET, normal, or hypermetabolic metabolism involving the LN (including the putamen and globus pallidus) and possibly the thalamus, motor cortex, and cerebellum can be seen in Parkinson's disease, whereas hypometabolism can be seen in parieto-occipital association areas and the dorsolateral prefrontal cortex (57) (58). A meta-analysis discovered reduced glucose metabolism in the bilateral inferior parietal cortex and left caudate nucleus in Parkinson's disease, which was associated with cognitive deficiencies and motor symptoms, respectively. When compared to PD and controls, MSA may show glucose hypometabolism in the putamen and brainstem, with or without hypometabolism in the cerebellum. Based on

the most impacted regions in these illnesses, glucose hypometabolism may be more prevalent in the bilateral putamen in MSA-P and bilateral cerebellum in MSA-C (57-59). Glucose hypometabolism was observed in the caudate/basal ganglia, midbrain, and thalamus, as well as the anterior cingulate, frontal, and primary motor cortices in PSP compared to controls. PSP patients had midbrain hypometabolism, which was shown as an oval or round region on 18F-FDG-PET and may suggest midbrain atrophy, compared to MSA and CBS patients.

PET imaging can also be used for other neurological functions such as neuropathology which detects pathological conditions such as deposits of proteins e.g., amyloid, tau, alpha-synuclein, etc (60). PET imaging can also be used for screening neuroinflammation in parkinsonian disorders.

Transcranial B-mode sonographic imaging:

Echogenicity in substantia nigra:

Increased echogenicity of the SN is prevalent in Parkinson's disease, and this can be seen at the mesencephalic plane as an expanded, lighter (i.e., weakly echogenic) patch inside the darker mesencephalon. Increased SN echogenicity is reported in PD patients with LRRK2 and GBA mutations (61), similar to idiopathic PD. Although the exact cause of SN hyperechogenicity is unknown, it is most likely owing to nigral disease and the concomitant increase of free (unbound) iron inside the SN.

SN hyperechogenicity may be present in preclinical phases, as discovered in people at high risk of Parkinson's disease, such as those with a family history of the disease. Over 5 years, the region of SN hyperechogenicity remained steady in PD, suggesting that this feature may be considered an early "trait" indication of vulnerability rather than a marker of progression in PD (62). Indeed, research has not consistently found a link between SN hyperechogenicity and illness severity or duration. One disadvantage of TCS is that 10% of participants do not have an appropriate bone window for imaging. It is also insufficiently specific, as up to 8% of senior normals and 16% of essential tremor sufferers have midbrain hyperechogenicity (63). Increased echogenicity of the SN, especially when significant, has been shown to distinguish PD cases from atypical PS (PSP and MSA as a group) with high sensitivity (91%) and specificity (82–96%). When skilled examiners are available, this technique can be useful in distinguishing between PD and atypical PS. Patients with DLB and PDD, on the other hand, present with hyperechogenic SN at frequencies comparable to those seen in Parkinson's

disease. For example, 80 percent of DLB cases had bilateral hyperechogenic SN, implying that the differential diagnosis in PDD/DLB is dependent on additional clinical characteristics and diagnostic biomarkers (2).

In conclusion, these findings imply that transcranial ultrasonography exams of the midbrain could be a simple and inexpensive method for confirming a clinical diagnosis of Parkinson's disease. More research is needed to establish its significance as a screening tool for identifying those at risk of the disease.

CONCLUSION:

A precise diagnosis of Parkinson's disease is needed for its management and to decide the therapeutic regimen. Though there are some advanced imaging techniques available, none of them can accurately confirm a diagnosis of PD. Using multiple tests for diagnosing PD along with a differential diagnosis seems to be advantageous. Genetic testing is only effective in some cases and due to its expensive costs, it is rarely used in diagnosis. Distinguishing between PD and other parkinsonian disorders is possible with the use of different imaging studies, but a high level of expertise is required. Further advancement in biomarkers for early detection of the disease with help of present imaging techniques may provide a better future for diagnosing PD.

ABBREVIATIONS:

PD- Parkinson's disease

SN- Substantia nigra

PSP- Progressive supranuclear palsy

MSA- Multisystem atrophy

DLB- Dementia with Lewy body

PDD- Parkinson's disease dementia

PS- Parkinsonian syndrome

CBS- Corticobasal syndrome

MSA-P- Multisystem atrophy parkinsonian type

MSA-C- Multisystem atrophy cerebellar type.

ACKNOWLEDGEMENT: -

We, the authors, are pleased to thank the Management of Oriental College of Pharmacy, Sanpada, Navi Mumbai- 400705, our Guide Dr. Mrs Vanita G. Kanse and Principal Dr. Mrs. Sudha Rathod.

CONFLICT OF INTEREST: -

There are no conflicts of interest among any of the authors of this paper.

REFERENCES:

1. Statistics [Internet]. Parkinson's Foundation. [Cited 2022 March 25]. Available from: <https://www.parkinson.org/Understanding-Parkinsons/Statistics>
2. Saeed U, Lang A, Masellis M. Neuroimaging Advances in Parkinson's disease and Atypical Parkinsonian Syndromes. *Frontiers in Neurology*. 2020; 11.
3. Kalia L, Lang A. Parkinson's disease. *The Lancet*. 2015; 386(9996):896-912.
4. Juárez Olguín H, Calderón Guzmán D, Hernández García E, Barragán Mejía G. The Role of Dopamine and Its Dysfunction as a Consequence of Oxidative Stress. *Oxidative Medicine and Cellular Longevity*. 2016; 2016:1-13.
5. Calabresi P, Picconi B, Tozzi A, Di Filippo M. Dopamine-mediated regulation of corticostriatal synaptic plasticity. *Trends in Neurosciences*. 2007; 30(5):211-219.
6. Htike T, Mishra S, Kumar S, Padmanabhan P, Gulyás B. Peripheral Biomarkers for Early Detection of Alzheimer's and Parkinson's Diseases. *Molecular Neurobiology*. 2018; 56(3):2256-2277.
7. Braak staging - Wikipedia [Internet]. [En.wikipedia.org](https://en.wikipedia.org/wiki/Braak_staging). 2022 [cited 2022 March 25]. Available from: https://en.wikipedia.org/wiki/Braak_staging
8. Galpern W, Lang A. Interface between tauopathies and synucleinopathies: A tale of two proteins. *Annals of Neurology*. 2006; 59(3):449-458.
9. Klein C, Westenberger A. Genetics of Parkinson's disease. *Cold Spring Harbor Perspectives in Medicine*. 2012; 2(1):a008888-a008888.
10. Chen L, Feany M. α -Synuclein phosphorylation controls neurotoxicity and inclusion formation in a *Drosophila* model of Parkinson disease. *Nature Neuroscience*. 2005;8(5):657-663.
11. Berardelli A, Rothwell J, Thompson P. Pathophysiology of bradykinesia in Parkinson's disease. *Brain*. 2001; 124(11):2131-2146.
12. Cooper J, Sagar H, Tidswell P, Jordan N. Slowed central processing in simple and go/no-go reaction time tasks in Parkinson's disease. *Brain*. 1994; 117(3):517-529.
13. Giovannoni G, van Schalkwyk J, and Fritz V, Lees A. Bradykinesia akinesia inco-ordination test (BRAIN TEST): an objective computerised assessment of upper limb motor function. *Journal of Neurology, Neurosurgery & Psychiatry*. 1999; 67(5):624-629.
14. Bagheri H, Michel C, Mestre M, Cismondo S, O'Connell D, Senard J et al. A study of salivary secretion in Parkinson's disease. *Clinical Neuropharmacology*. 1999; 22(4):213-215.
15. Signs and symptoms of Parkinson's disease - Wikipedia [Internet]. [En.wikipedia.org](https://en.wikipedia.org/wiki/Signs_and_symptoms_of_Parkinson%27s_disease). [cited 2022 March 25]. Available from: https://en.wikipedia.org/wiki/Signs_and_symptoms_of_Parkinson%27s_disease
16. Jankovic J. Parkinson's disease: clinical features and diagnosis. *Journal of Neurology, Neurosurgery & Psychiatry*. 2008;79(4):368-376.
17. Parr-Brownlie L. Bradykinesia Induced by Dopamine D2 Receptor Blockade Is Associated with Reduced Motor Cortex Activity in the Rat. *Journal of Neuroscience*. 2005; 25(24):5700-5709.

18. Turner R, Grafton S, McIntosh A, DeLong M, Hoffman J. The functional anatomy of parkinsonian bradykinesia. *NeuroImage*. 2003; 19(1):163-179.
19. Shulman L, Singer C, Bean J, Weiner W. Internal tremor in patients with Parkinson's disease. *Movement Disorders*. 1996; 11(1):3-7.
20. Jankovic J, Schwartz K, Ondo W. Re-emergent tremor of Parkinson's disease. *Journal of Neurology, Neurosurgery & Psychiatry*. 1999; 67(5):646-650.
21. Riley D, Lang A, Blair R, Birnbaum A, Reid B. Frozen shoulder and other shoulder disturbances in Parkinson's disease. *Journal of Neurology, Neurosurgery & Psychiatry*. 1989; 52(1):63-66.
22. Ashour R, Tintner R, Jankovic J. Striatal deformities of the hand and foot in Parkinson's disease. *The Lancet Neurology*. 2005;4(7):423-431.
23. Ashour R, Jankovic J. Joint and skeletal deformities in Parkinson's disease, multiple system atrophy, and progressive supranuclear palsy. *Movement Disorders*. 2006;21(11):1856-1863.
24. Askmark H, Eeg-Olofsson K, Johansson A, Nilsson P, Olsson Y, Aquilonius S. Parkinsonism and Neck Extensor Myopathy. *Archives of Neurology*. 2001; 58(2):232-237.
25. Djaldetti R, Melamed E. Camptocormia in Parkinson's disease: new insights. *Journal of Neurology, Neurosurgery & Psychiatry*. 2006; 77(11):1205-1205.
26. Azher S, Jankovic J. Camptocormia: Pathogenesis, classification, and response to therapy. *Neurology*. 2005; 65(3):355-359.
27. Williams D. Predictors of falls and fractures in bradykinetic rigid syndromes: a retrospective study. *Journal of Neurology, Neurosurgery & Psychiatry*. 2006; 77(4):468-473.
28. Giladi N, McDermott M, Fahn S, Przedborski S, Jankovic J, Stern M et al. Freezing of gait in PD: Prospective assessment in the DATATOP cohort. *Neurology*. 2001; 56(12):1712-1721.
29. Macht M, Kaussner Y, Möller J, Stiasny-Kolster K, Eggert K, Krüger H et al. Predictors of freezing in Parkinson's disease: A survey of 6,620 patients. *Movement Disorders*. 2007; 22(7):953-956.
30. Boghen D. Apraxia of lid opening. *Neurology*. 1997; 48(6):1491-1494.
31. Bloem B, Hausdorff J, Visser J, Giladi N. Falls and freezing of gait in Parkinson's disease: A review of two interconnected, episodic phenomena. *Movement Disorders*. 2004; 19(8):871-884.
32. Senard J, Rai S, Lapeyre-Mestre M, Brefel C, Rascol O, Rascol A et al. Prevalence of orthostatic hypotension in Parkinson's disease. *Journal of Neurology, Neurosurgery & Psychiatry*. 1997; 63(5):584-589.
33. Swinn L, Schrag A, Viswanathan R, Bloem B, Lees A, Quinn N. Sweating dysfunction in Parkinson's disease. *Movement Disorders*. 2003; 18(12):1459-1463.
34. Hely M, Morris J, and Reid W, Trafficante R. Sydney Multicenter Study of Parkinson's disease: non-L-dopa-responsive problems dominate at 15 years. *Movement Disorders*. 2005; 20(2):190-199.
35. Aarsland D, Bronnick K, Ehrt U, De Deyn P, Tekin S, Emre M et al. Neuropsychiatric symptoms in patients with Parkinson's disease and dementia: frequency, profile and associated care giver stress. *Journal of Neurology, Neurosurgery & Psychiatry*. 2007; 78(1):36-42.
36. Ravina B, Camicioli R, Como P, Marsh L, Jankovic J, Weintraub D et al. The impact of depressive symptoms in early Parkinson disease. *Neurology*. 2007; 69(4):342-347.
37. Palmiter R. Is dopamine a physiologically relevant mediator of feeding behavior?. *Trends in Neurosciences*. 2007; 30(8):375-381.
38. Miyasaki J, Al Hassan K, Lang A, Voon V. Punding prevalence in Parkinson's disease. *Movement Disorders*. 2007; 22(8):1179-1181.
39. Gibb W, Lees A. The relevance of the Lewy body to the pathogenesis of idiopathic Parkinson's disease. *Journal of Neurology, Neurosurgery & Psychiatry*. 1988; 51(6):745-752.
40. Gelb D, Oliver E, Gilman S. Diagnostic Criteria for Parkinson Disease. *Archives of Neurology*. 1999; 56(1):33-39.
41. Deuschl G, Bain P, Brin M. Consensus Statement of the Movement Disorder Society on Tremor. *Movement Disorders*. 2008; 13(S3):2-23.
42. Louis E, Levy G, Côte L, Mejia H, Fahn S, Marder K. Clinical Correlates of Action Tremor in Parkinson Disease. *Archives of Neurology*. 2001; 58(10):1630-1634.

43. Tolosa E, Wenning G, Poewe W. The diagnosis of Parkinson's disease. *The Lancet Neurology*. 2006; 5(1):75-86.
44. McKeith I, Mintzer J, Aarsland D, Burn D, Chiu H, Cohen-Mansfield J et al. Dementia with Lewy bodies. *The Lancet Neurology*. 2004; 3(1):19-28.
45. Steele J, Richardson J, Olszewski J. Progressive Supranuclear Palsy: A Heterogeneous Degeneration Involving the Brain Stem, Basal Ganglia and Cerebellum with Vertical Gaze and Pseudobulbar Palsy, Nuchal Dystonia and Dementia. *Seminars in Neurology*. 2014; 34(02):129-150.
46. Litvan I, Agid Y, Calne D, Campbell G, Dubois B, Duvoisin R et al. Clinical research criteria for the diagnosis of progressive supranuclear palsy (Steele-Richardson-Olszewski syndrome). *Neurology*. 1996; 47(1):1-9.
47. Colosimo C, Albanese A, Hughes A, de Bruin V, Lees A. Some Specific Clinical Features Differentiate Multiple System Atrophy (Striatonigral Variety) From Parkinson's disease. *Archives of Neurology*. 1995; 52(3):294-298.
48. Poewe W, Seppi K, Tanner C, Halliday G, Brundin P, Volkman J et al. Parkinson disease. *Nature Reviews Disease Primers*. 2017; 3(1).
49. Tinsley R, Kotschet K, Modesto D, Ng H, Wang Y, Nagley P et al. Sensitive and specific detection of α -synuclein in human plasma. *Journal of Neuroscience Research*. 2010; 88(12):2693-2700.
50. Garnett E, Firnau G, Nahmias C. Dopamine visualized in the basal ganglia of living man. *Nature*. 1983; 305(5930):137-138.
51. Stoessel A, Lehericy S, Strafella A. Imaging insights into basal ganglia function, Parkinson's disease, and dystonia. *The Lancet*. 2014; 384(9942):532-544.
52. Mahlkecht P, Hotter A, Hussl A, Esterhammer R, Schocke M, Seppi K. Significance of MRI in Diagnosis and Differential Diagnosis of Parkinson's Disease. *Neurodegenerative Diseases*. 2010;7(5):300-318.
53. Scherfler C, Göbel G, Müller C, Nocker M, Wenning G, Schocke M et al. Diagnostic potential of automated subcortical volume segmentation in atypical Parkinsonism. *Neurology*. 2016; 86(13):1242-1249.
54. Brücke T, Wenger S, Asenbaum S, Fertl E, Pfafflmeyer N, Müller C et al. Dopamine D2 receptor imaging and measurement with SPECT. *Advances in Neurology*. 1993; 60:494-500.
55. Seppi K, Schocke M, Donnemiller E, Esterhammer R, Kremser C, Scherfler C et al. Comparison of diffusion-weighted imaging and [123I]IBZM-SPECT for the differentiation of patients with the Parkinson variant of multiple system atrophy from those with Parkinson's disease. *Movement Disorders*. 2004; 19(12):1438-1445.
56. Catafau A, Tolosa E. Impact of dopamine transporter SPECT using 123I-Ioflupane on diagnosis and management of patients with clinically uncertain parkinsonian syndromes. *Movement Disorders*. 2004; 19(10):1175-1182.
57. Eckert T, Barnes A, Dhawan V, Frucht S, Gordon M, Feigin A et al. FDG PET in the differential diagnosis of parkinsonian disorders. *NeuroImage*. 2005; 26(3):912-921.
58. Tripathi M, Dhawan V, Peng S, Kushwaha S, Batla A, Jaimini A et al. Differential diagnosis of parkinsonian syndromes using F-18 fluorodeoxyglucose positron emission tomography. *Neuroradiology*. 2013; 55(4):483-492.
59. Albrecht F, Ballarini T, Neumann J, Schroeter M. FDG-PET hypometabolism is more sensitive than MRI atrophy in Parkinson's disease: A whole-brain multimodal imaging meta-analysis. *NeuroImage: Clinical*. 2019; 21:101594.
60. Zaleski N, Botha H, Whitwell J, Lowe V, Dickson D, Josephs K. FDG-PET in pathologically confirmed spontaneous 4R-tauopathy variants. *Journal of Neurology*. 2014; 261(4):710-716.
61. Barrett M, Hagenah J, Dhawan V, Peng S, Stanley K, Raymond D et al. Transcranial sonography and functional imaging in glucocerebrosidase mutation Parkinson disease. *Parkinsonism & Related Disorders*. 2013; 19(2):186-191.
62. Berg D, Merz B, Reiners K, Naumann M, Becker G. Five-year follow-up study of hyperechogenicity of the substantia nigra in Parkinson's disease. *Movement Disorders*. 2005; 20(3):383-385.
63. Brooks D. Parkinson's disease: Diagnosis. *Parkinsonism & Related Disorders*. 2012; 18:S31-S33.