WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.084
Volume 10, Issue 3, 854-865. Review Article ISSN 2277– 7105

THE REVIEW OF PARKINSON'S DISEASE

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Article Received on
08 Jan. 2020,

Revised on 29 Jan. 2021,
Accepted on 19 Feb. 2021

DOI: https://doi.org/10.17605/OSF.IO/RGEYF

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ABSTRACT

Parkinson's disease (PD) is a progressive, neurodegenerative disorder of aging that affects both motor and cognitive function. The etiology of PD is mostly unknown, but it likely involves both genetic and environmental factors. In contrast, the network-level pathology of PD is reasonably well understood. There are quite effective medications to treat the motor symptoms of PD. In addition, medication-resistant PD is routinely treated with **deep brain stimulation** (DBS). Despite the clinical success of DBS in PD, the mechanisms of action of DBS are poorly understood. In this chapter, we will first review the basic clinical aspects of PD, and then we will consider the network-level pathology. Finally, we will discuss the effect of DBS on the diseased networks. Parkinson's disease (PD) is a common neurodegenerative disease. Early concepts looking at PD as purely a motor disorder have led the way to seeing it as a much more widespread neurological disease with affective, cognitive, and autonomic manifestations. The etiology of PD is still unknown, but important steps have been made to understand its pathogenesis . To a large extent, these derived from the identification of genetic variants of PD. Mutations in several genes have been discovered that cause monogenic PD, while GWAS has identified other loci associated with sporadic disease.

INTRODUCTION

Parkinsons disease (PD) is a progressive neurodegenerative disorder initially described in 1817 by Dr. James Parkinson in “An Essay on the Shaking Palsy.” PD is characterized clinically by the asymmetric and slowly progressive onset of parkinsonism benefiting from dopaminergic medication, and pathologically by the loss of dopaminergic cells and

occurrence of Lewy bodies in the substantia nigra and specific brain stem areas.

Typically, PD presents in the 60s with a slowly progressive bradykinesia (slowness) tremor at rest, and rigidity affecting one of the limbs, that benefits from dopaminergic medication, in the absence of atypical features (i.e., falls, dementia, or autonomic features early in the course of the disease).

The prevalence of PD is 200–300 cases per 100 000 people, and in the United States about 1 million persons are affected. The annual incidence is approximately 20 new cases per 100 000 people, and about 60 000 Americans are diagnosed with PD each year. The likelihood of developing PD increases with age.

PD typically develops in the 60s, but can occur at younger ages. Approximately 10% of all patients develop symptoms before age 40. PD is usually a sporadic disease but is hereditary in 10% of the patients. Men are slightly more frequently affected than women.

Epidemiology

PD has an annual prevalence of 48–69 per 1000 persons per year, with an average age at onset of 60 years. In the United States, there are 500,000 to 1 million cases of PD.

The annual incidence is between 25 and 55% per year affecting up to 0.3% of the general population. Prevalence increases with age, thus those persons older than 65 years have a PD prevalence of 14.9%, increasing to 29.5% and 52.4% by ages 75 and 85 years, respectively. Only 5% will have symptoms before age 40 years. In a Chinese study, Zhang et al.

Reported a PD prevalence of 1.7% in those older than 65 years. Considering that China has the world's largest population, the numbers are staggering. There are approximately 1.7 million persons with this neurodegenerative condition in China. The burden to Chinese society is tantamount to the PD burden known to the United States, but in a country with a dissimilar medical system and lack of access to Western-style medical care, this burden is greater than in the United States, where the absolute number of PD cases is smaller. In this study, the number of persons unaware of having the disease was 48%, with a higher incidence in those living in rural areas, suggesting that a large segment of the world population has no access to medical care.

In a European prevalence study, the overall prevalence for those older that 65 years was 1.8, increasing by 0.6 for those age 65–69 years and to 2.6 for those 85.

Depending on the criteria used for the diagnosis of PD, the actual incidence of this condition may vary across different age-groups, but Bower et al. demonstrated that using the most accepted diagnostic clinical criteria for PD, the incidence indeed increases with age. Von Campenhausen et al.[20] studied the prevalence and incidence for PD in Europe and found a PD prevalence of 108–257/100,000 and an incidence of 11–19/100,000 per year. When only older age-groups (those older than 60 years) were included, rates of prevalence and incidence were much higher (1280–1500/100,000 and 346/100,000, respectively). The authors noted that the large variations in rates might have resulted from environmental and genetic factors and diagnostic criteria and differences in methodology, survey design, case-finding strategies, and age distributions.

PD is mostly a disease of middle age and the elderly, so substantial direct and indirect costs may be associated with the illness, including lack of productivity, uncompensated informal care-giving by family members, as well as direct medical care, medications, and supplies. Increased mortality has been a concern for many patients with PD. It has been argued that the introduction of l-dopa decreased the higher than expected mortality rate observed before the use of this medication. Marras et al.

Addressed survival in patients with PD in a 13-year follow-up study using the Deprenyl and Tocopherol Antioxidative Therapy of Parkinson's disease (DATATOP) cohort. The authors found the mortality rate of patients with PD to be the same as that of the general population. In the same study, the authors found increasing age, male gender, more pack-years smoking, lower Mini-Mental State Examination (MMSE) scores, extensor–plantar responses, and the presence of cardiac, pulmonary, and urological co-morbidities strongly associated with a higher than expected mortality in those patients with PD who have some of these characteristics. Patients with PD who were full-time employees had a better survival.

Duration of disease and tremor were not associated with increased mortality. PD-specific variables associated with increased mortality were increased symmetry of parkinsonism , presence and severity of gait dysfunction, rate of progression of symptoms before baseline evaluation, higher Hoehn and Yahr stage, and increased Unified Parkinson's Disease Rating Scale (UPDRS) total, motor, and activities of daily living (ADL) scores.

In addition, those patients whom the investigator thought that PD was the most likely diagnosis did better than those in which the diagnosis was multiple-system atrophy, progressive supranuclear palsy, atypical parkinsonism of uncertain type, and diffuse Lewy body disease.

DESCRIPTION

Parkinson's disease (PD) is a progressive neurodegenerative disorder whose pathologic hallmark is loss of dopaminergic neurons in the substantia nigra pars compacta. The cardinal motor signs of PD are tremor, rigidity, bradykinesia/akinesia, and a gait disorder characterized by a flexed posture and short, shuffling steps. The diagnosis is made clinically by noting at least two of these characteristic motor signs in addition to a clear-cut response to antiparkinsonian medications. Patients may also develop postural instability and freezing, a phenomenon characterized by a sudden inability to continue or initiate movement. Decreased associated movements (masked facies, decreased eye blink, and reduced arm swing) are common early *signs* of PD.

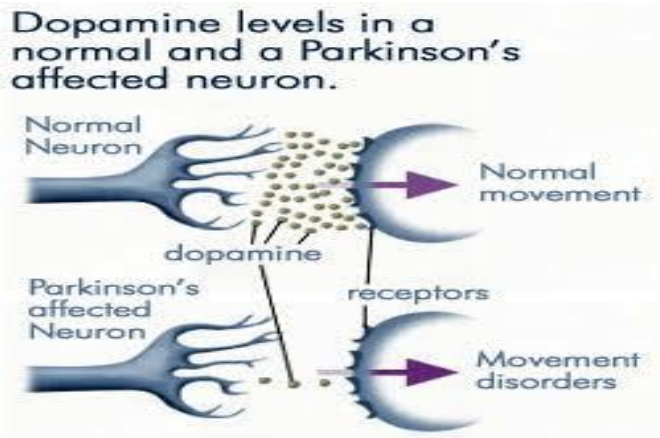
Hypophonia; micrographia; and difficulty with fine motor control (buttoning buttons, handling utensils, shaving or applying makeup), getting out of a chair, or rolling over in bed at night are common early *complaints* of PD patients. Some PD patients may present with early morning foot or toe dystonia. Motor complications in the form of unpredictable "on-off" periods (motor fluctuations) and drug-induced involuntary movements (dyskinesia or dystonia) occur later in the disorder, are associated with long-term drug therapy, and pose a significant challenge for the clinician who must try to maintain the therapeutic response in a progressively more narrow therapeutic window.

Nonmotor symptoms are also common in PD. Depression occurs in approximately 50% of patients with PD and may present at any time in the course of the disease. Visual and rarely auditory hallucinations can also occur in association with antiparkinsonian medication in patients who have had PD for many years. Dementia is not typical in early idiopathic PD but may develop in the later stages of the disease. Other symptoms that may develop or be associated with PD include autonomic insufficiency, difficulty with articulation, frequent urination, seborrhea, dysphagia, constipation, and ill-defined sensory complaints often reported as a deep aching sensation that in some patients may be quite painful.

PD occurs most commonly in older patients, but it is not infrequent in younger adults and, although rare, may occur in juveniles. With younger patients, dystonic symptoms are more common. About 15% of cases are familial.

Parkinson's disease (PD)

Simply Parkinson's is a long-term degenerative disorder of the central nervous system that mainly affects the motor system. The symptoms usually emerge slowly and, as the disease worsens, non-motor symptoms become more common. The most obvious early symptoms are tremor, rigidity, slowness of movement, and difficulty with walking.



Cognitive and behavioral problems may also occur with depression, anxiety, and apathy occurring in many people with PD. Parkinson's disease dementia becomes common in the advanced stages of the disease. Those with Parkinson's can also have problems with their sleep and sensory systems.

The motor symptoms of the disease result from the death of cells in the substantia nigra, a region of the midbrain, leading to a dopamine deficit. The cause of this cell death is poorly understood, but involves the build-up of misfolded proteins into Lewy bodies in the neurons. Collectively, the main motor symptoms are also known as "parkinsonism" or a "parkinsonian syndrome".

CLSSIFICATION

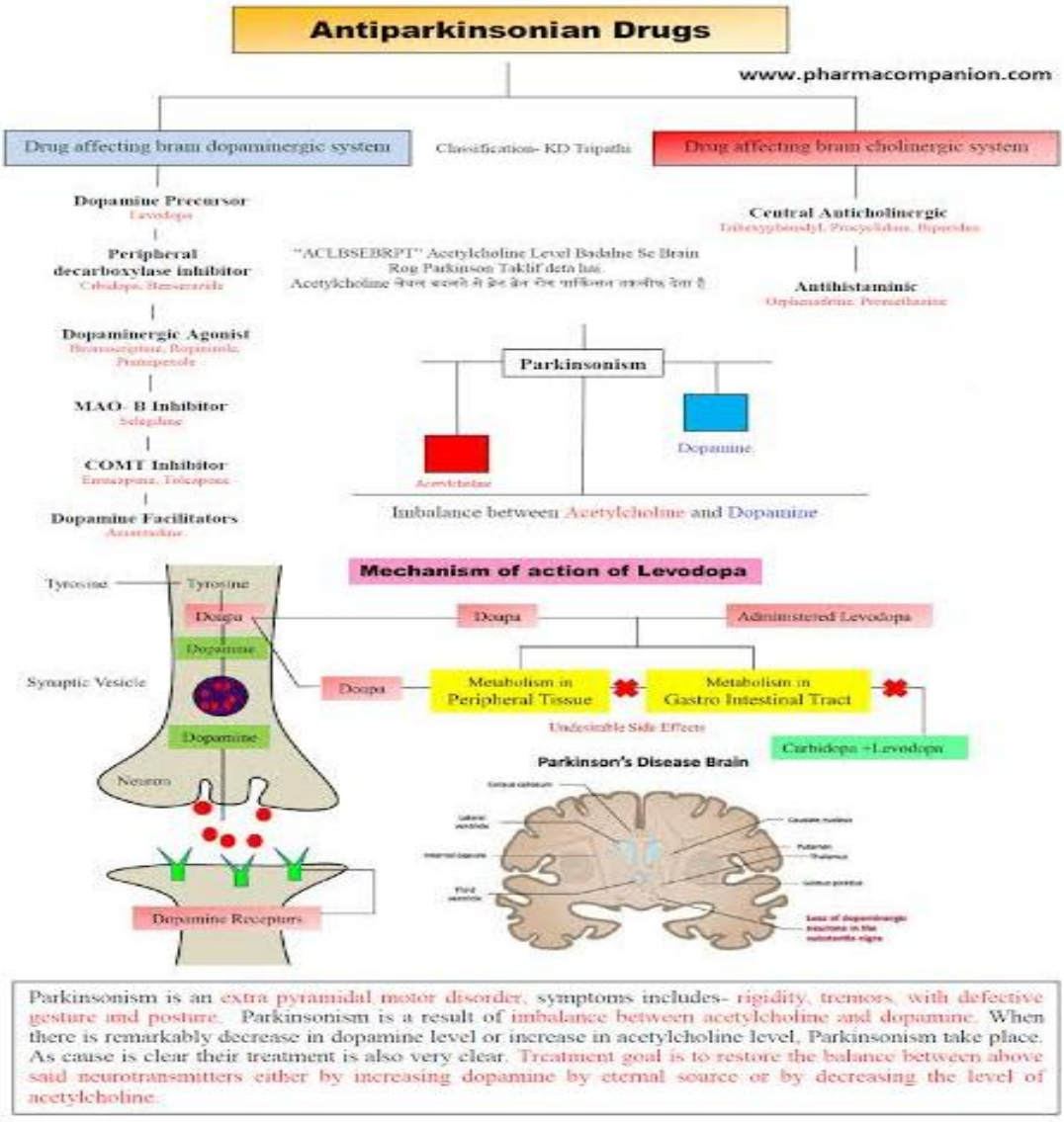
Parkinson's disease is the most common form of parkinsonism and is sometimes called "idiopathic parkinsonism", meaning parkinsonism with no identifiable cause. Scientists sometimes refer to Parkinson’s disease as a type of neurodegenerative disease called synucleinopathy due to an abnormal accumulation of the protein alphasynuclein in the brain.

The synucleinopathy classification distinguishes Parkinson's disease from other neurodegenerative diseases, such as Alzheimer's disease, where the brain accumulates a different protein known as the tau protein. Considerable clinical and pathological overlap exists between tauopathies and synucleinopathies, however there are also differences.

In contrast to Parkinson's disease, people with Alzheimer's disease most commonly experience memory loss. The cardinal signs of Parkinson's disease (slowness, tremor, stiffness, and postural instability) are not normal features of Alzheimer's.

Attempts to classify Parkinson's disease into different subtypes have been made, with focus put on age of onset, progression of symptoms, and dominance of tremor. None have currently been widely adopted as a complete model.

ANTIPARKINSON'S DRUG



SIGN AND SYMPTOMS

The most recognizable symptoms in Parkinson's disease are movement ("motor") related. Non-motor symptoms, which include autonomic dysfunction, neuropsychiatric problems (mood, cognition, behavior or thought alterations), and sensory (especially altered sense of smell) and sleep difficulties, are also common. Some of these non-motor symptoms may be present at the time of diagnosis.

A) ***Motor***

Four motor symptoms are considered cardinal in PD: tremor, slowness of movement (bradykinesia), rigidity, and postural instability. The most common presenting sign is a coarse slow tremor of the hand at rest which disappears during voluntary movement of the affected arm and in the deeper stages of sleep.

It typically appears in only one hand, eventually affecting both hands as the disease progresses. Frequency of PD tremor is between 4 and 6 hertz (cycles per second). A feature

of tremor is pill-rolling, the tendency of the index finger and thumb to touch and perform together a circular movement.

The term derives from the similarity between the movement of people with PD and the early pharmaceutical technique of manually making pills. Bradykinesia (slowness of movement) is found in every case of PD, and is due to disturbances in motor planning of movement initiation, and associated with difficulties along the whole course of the movement process, from planning to initiation to execution of a movement. Performance of sequential and simultaneous movement is impaired.

Bradykinesia is the most handicapping symptom of Parkinson's disease leading to difficulties with everyday tasks such as dressing, feeding, and bathing. It leads to particular difficulty in carrying out two independent motor activities at the same time and can be made worse by emotional stress or concurrent illnesses. Paradoxically people with Parkinson's disease can often ride a bicycle or climb stairs more easily than walk on a level. While most physicians may readily notice bradykinesia, formal assessment requires a person to do repetitive movements with their fingers and feet.

Rigidity is stiffness and resistance to limb movement caused by increased muscle tone, an excessive and continuous contraction of muscles. In parkinsonism, the rigidity can be uniform, known as "lead-pipe rigidity, "or ratchety, known as "cogwheel rigidity."

The combination of tremor and increased tone is considered to be at the origin of cogwheel rigidity. Rigidity may be associated with joint pain; such pain being a frequent initial manifestation of the disease.

B) ***Neuropsychiatric***

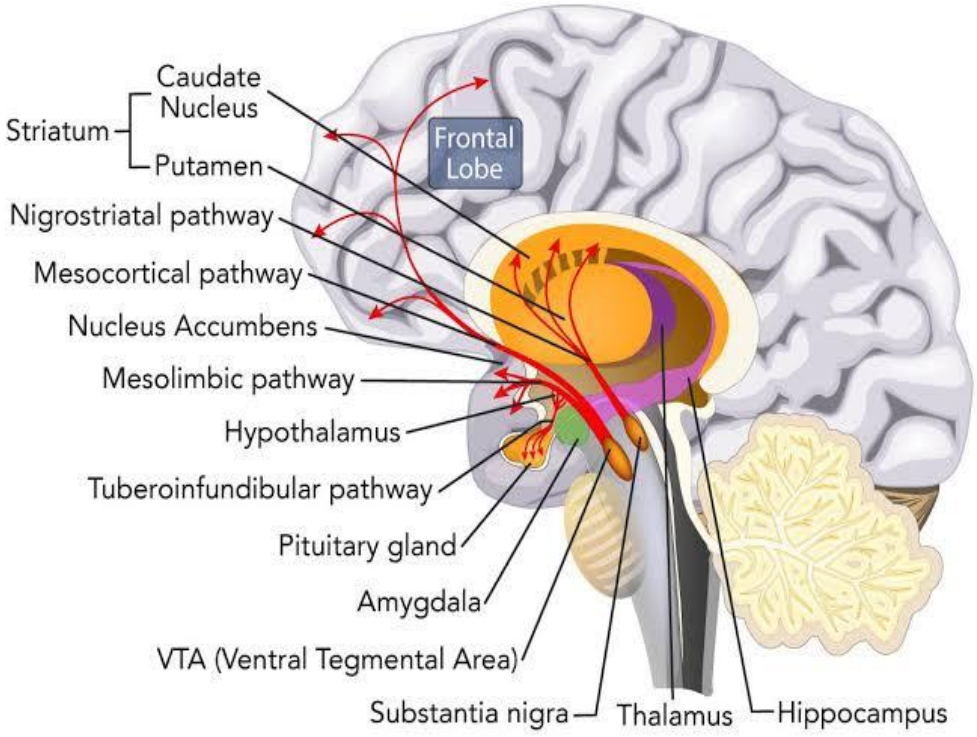
Parkinson's disease can cause neuropsychiatric disturbances, which can range from mild to severe. This includes disorders of cognition, mood, behavior, and thought.

Cognitive disturbances can occur in the early stages of the disease and sometimes prior to diagnosis, and increase in prevalence with duration of the Disesase.

The most common cognitive deficit in PD is executive dysfunction, which can include problems with planning, cognitive flexibility, abstract thinking, rule acquisition, inhibiting inappropriate actions, initiating appropriate actions, working memory, and control of

attention.

Other cognitive difficulties include slowed cognitive processing speed, impaired recall and impaired perception and estimation of time. Nevertheless, improvement appears when recall is aided by cues.



Visuospatial difficulties are also part of the disease, seen for example when the individual is asked to perform tests of facial recognition and perception of the orientation of drawn lines.

C) ***Psychosis***

Psychosis can be considered a symptom with a prevalence at its widest range from 26 to 83%. Hallucinations or delusions occur in approximately 50% of people with PD over the course of the illness, and may herald the emergence of dementia.

These range from minor hallucinations – "sense of passage" (something quickly passing beside the person) or "sense of presence" (the perception of something/someone standing just to the side or behind the person) – to full blown vivid, formed visual hallucinations and paranoid ideation.

Auditory hallucinations are uncommon in PD, and are rarely described as voices. It is now believed that psychosis is an integral part of the disease.

A psychosis with delusions and associated delirium is a recognized complication of anti-Parkinson drug treatment and may also be caused by urinary tract infections (as frequently occurs in the fragile elderly), but drugs and infection are not the only factors, and underlying brain pathology or changes in neurotransmitters or their receptors (e.g., acetylcholine, serotonin) are also thought to play a role in psychosis in PD.

D) *Behavior and mood*

Behavior and mood alterations are more common in PD without cognitive impairment than in the general population, and are usually present in PD with dementia. The most frequent mood difficulties are depression, apathy, and anxiety.

E) *Depression*

Has been estimated to appear in anywhere from 20 to 35% of people with PD, and can appear at any stage of the disease. In Parkinson's, depression can manifest with symptoms that are common to the disease process (fatigue, insomnia, and difficulty with concentration) which makes diagnosis difficult.

The imbalance and change in dopamine, serotonin, and noradrenergic hormones are known to be a primary cause of depression in PD affected people. Another cause is the functional impairment that is caused by the disease.

Symptoms of depression can include loss of interest, sadness, guilt, feelings of helplessness/hopelessness/guilt, and suicidal ideation.

F) *Apathy And Anhedonia*

An be defined as a loss of motivation and an impaired ability to experience pleasure, respectively. They are symptoms classically associated with depression however differ in PD affected people in treatment, mechanism, and doesn't always occur with depression. Apathy presents in around 16.5-40%. Symptoms of apathy include reduced initiative/interests in new activities or the world around them. emotional indifference, and loss of affection or concern for others. Apathy is associated with deficits in cognitive functions including executive and verbal memory.

G) Other

Sleep disorders are a feature of the disease and can be worsened by medications. Symptoms can manifest as daytime drowsiness, disturbances in REM sleep, or insomnia.

REM behavior disorder (RBD), in which people act out dreams, sometimes injuring themselves or their bed partner, may begin many years before the development of motor or cognitive features of PD or DLB.

CAUSE

Many risk factors have been proposed, sometimes in relation to theories concerning possible mechanisms of the disease; however, none have been conclusively proven.

The most frequently replicated relationships are an increased risk in those exposed to pesticides, and a reduced risk in smokers. There is a possible link between PD and H. pylori infection that can Causes prevent the absorption of some drugs including levodopa.

PALLIATIVE CARE

Palliative care is specialized medical care for people with serious illnesses, including Parkinson's. The goal of this speciality is to improve quality of life for both the person with Parkinson's and the family by providing relief from the symptoms, pain, and stress of illnesses.

As Parkinson's is not a curable disease, all treatments are focused on slowing decline and improving quality of life, and are therefore palliative in nature. Palliative care should be involved earlier, rather than later in the disease course.

Palliative care specialists can help with physical symptoms, emotional factors such as loss of function and jobs, depression, fear, and existential concerns. Along with offering emotional support to both the affected person and family, palliative care serves an important role in addressing goals of care. People with Parkinson's may have many difficult decisions to make as the disease progresses such as wishes for feeding tube, non-invasive ventilator, and tracheostomy; wishes for or against cardiopulmonary resuscitation; and when to use hospice care.

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