

Review Article

Neurodegenerative Disease: Parkinson's -A Comprehensive Review

Abstract

The most prevalent neurodegenerative condition is Parkinson's Disease. There are three primary processes for the loss of neurons that may operate alone or in concert to result in neurodegeneration. This lethal trifecta of excitotoxicity, metabolic compromise, and oxidative stress results in necrotic and apoptotic neuronal cell death. It is thought that elements of each of these three pathways contribute to the neurodegeneration as seen in Parkinson's illnesses. Promoting neuronal development and function or preventing neurotoxic processes are typical tactics used to rescue or protect damaged neurons. Many other neuroprotective drugs have been tested in depth using animal models that mimic this illness. The care of Parkinson's disease (PD) is projected to become a more significant and difficult component of medical practice for neurologists and general practitioners as the population ages.

With the discovery of many gene mutations over the past ten years, which may provide insight into the mechanisms underlying the pathogenesis of sporadic cases of PD, our understanding of the disease's pathophysiology has evolved. The diagnosis of Parkinson's disease (PD) is still primarily clinical, thus it's critical to recognize the early symptoms as well as those that point to additional causes of parkinsonism.

Along with a deeper understanding of non-motor problems, therapies have rapidly expanded for both the early and late stages of the illness. The National Institute for Health and Clinical Excellence (NICE) in the UK has produced guidelines for the diagnosis and management of patients with PD.

Keywords: Neurodegenerative disease; Parkinson's; Dopamine; hypokinesia; neurotransmitter

Introduction

Parkinson's disease is a neurological illness that worsens with time and is caused due to deficiency in the brain known as dopamine. Dopaminergic cell loss causes lower levels of this neurotransmitter, which is important in motivation, memory, locomotion, and other behaviors, to be present in PD brains [1]. Dopamine depletion in the PD brain causes movement dysfunction and possibly the cognitive deficiency found in some PD patients [2]. Although roughly 5% to 10% of Parkinson's patients suffer onset before the age of 50, most Parkinson's patients first experience the disease beyond the age of 60. While not always hereditary, early-onset of Parkinson's disease has been linked to specific genetic changes i.e. Mutation in 6 genes (*SNCA*, *LRK2*, *PRKN*, *DJI*, *PINK1* and *ATP13A2*) in some cases.[3] Moreover, Parkinson's disease is pathologically marked by a loss of nigrostriatal dopaminergic innervation, but other neurons in the neural network are also affected by neurodegeneration, which is not just a problem for nigral dopaminergic neurons [4]. Because of its widespread underlying disease, PD is a very heterogeneous condition, and there is no accurate diagnostic technique at this time. The presence of two of the clinical signs of rigidity, postural instability, bradykinesia, resting tremor, or both are required for the diagnosis. A conclusive diagnosis of Parkinson's Disease can only be made through histological examination and the detection of Lewy bodies that contains α -Synuclein [5]. The main stay of treatment is using drugs that either work on striatal post-synaptic dopamine receptors or enhance dopamine levels in the striatum, which primarily aims to relieve symptoms numerous also additionally, various medicines are used to treat certain symptoms, such as depression or dementia because dopamine is not the only transmitter implicated in Parkinson's disease [6]. More studies and inventive medications are required to slow the progress of neurodegeneration or even to restore the lost dopaminergic cells, even though some are still in the early phases of human trials. The potential for the development of enzymes that modify disease is encouraging as our knowledge of the etiology of Parkinson's Disease expands, and new therapeutic targets are better understood [7].

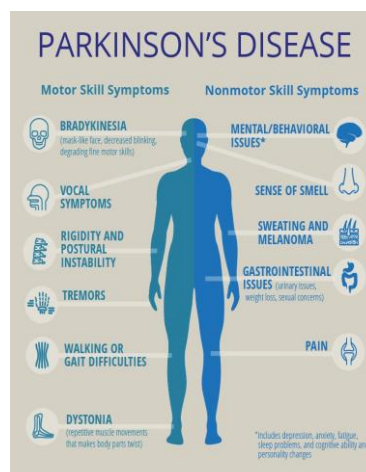


Fig1. Symptoms and Epidemiology of Parkinson's Disease[Reference8]

The Parkinson's Disease (PD) is a neurological condition that cannot be cured. Also, it results in unintentional or involuntary movements, such as tremors and stiffness, as well as balance and coordination problems [9]. Symptoms begin mild and becomes worsens over time. Additionally, people may experience depression, weariness, and changes in their behavior [10]. Most prominent signs and symptoms are mostly caused by the loss or death of nerve cells in the basal ganglia, an area of the brain that controls movement. These nerve cells or neurons produce a chemical known as dopamine, which is a crucial neurotransmitter in the brain [11].

Symptoms of Parkinson's Disease: Symptoms of this disease includes, Rigidity; muscular stiffness, which occurs when a muscle is tight for a long time, hypokinesia (motion that is slow), Tremor, Postural instability, Poor balance and coordination

Additional signs includes: Constipation or urinary issues; trouble swallowing, chewing and speaking; depression and other emotional disturbances [12].

Diagnosis of Parkinson's Disease

As PD cannot be diagnosed and no blood and laboratory tests are available in non-genetic cases.

- SPECT or DaTSCAN

These scans also provides an information on the functioning of various brain regions. A specific kind of imaging test called a SPECT which reveals the blood flow patterns to organs and tissues including muscles [13]. The loss of a certain type of brain cell that contains the neurotransmitter 'dopamine' is confirmed by professionals with the aid of a specific form of SPECT scan [14]. A dopamine transporter scan, or DaTSCAN, is used to differentiate between Alzheimer's Disease and between a type of dementia described as 'Dementia with Lewy bodies'. The majority of the time, Parkinson's is the cause of an aberrant DaTSCAN result, although it cannot be diagnosed with certainty [15].

A normal DaTSCAN can be useful in demonstrating that a person's symptoms, especially tremor, may not be related to Parkinson's disease but rather to another disorder, such as essential tremor.

- Recent research has shown that MRI can be used to detect and diagnose Parkinson's disease far sooner than conventional techniques [16]. In order to detect Parkinson's disease, MRIs scan the brain for particular markers. These signs are frequently present even before Parkinson's symptoms appear [17].

Medications for Parkinson's Disease

- Levodopa is the primary therapy for Parkinson's disease. To refill the declining ranges of dopamine inside the brain, levodopa is transformed into dopamine via nerve cells. [18]. Dopamine Agonists-replace the brain's dopamine and, have a comparable but less potent effect when compared to levodopa.
- Monoamine Oxidase-B inhibitors, including selegiline and rasagiline- Additionally, by preventing the effects of monoamine oxidase-B, an enzyme or brain substance that degrades dopamine, which increase dopamine levels. Apomorphine- is an injectable, short-acting dopamine agonist indicated for prompt relief [19].
- Catechol O-methyltransferase (COMT) inhibitors- Inhibitors of COMT stands for catechol O-methyltransferase [20]. The two main drugs in this group are entacapone and opicapone. The effects of levodopa therapy are prolonged by this medication because it prevents an enzyme from degrading dopamine [21].
- Nuplazid (Pimavanserin)-Patients with Parkinson's disease who develops hallucinations and delusions are treated with this drug [22].
- Moreover, cytokines such as IL-2, IL-4, IL-6, IL-10, and TNF- α increase in the serum of PD Patients an association between systemic markers of inflammation and

Condition	History	Clinical features	Investigations	Management
Drug-induced parkinsonism	Exposure to drugs mainly neuroleptic treatment and anti-emetics	May be associated with akathisia and Oro-mandibular dystonia	Based on history	Discontinue offending drug, Anticholinergic drugs may be helpful for tremor
Multisystem Atrophy	Parkinsonism and or gait unsteadiness with or without autonomic dysfunction	Orthostatic Hypotension, absence of tremor, symmetrical signs, cerebellar features, poor response to levodopa	MRI brain sphincter EMG	Levodopa trial, amantadine measures to control postural hypotension, E.g.- fludrocortisone

idiopathic PD risks has been reported [23].

Dementia with Lewy Bodies	Dementia occurring before or concurrently with parkinsonism	Visual hallucinations	MRI brain, psychometry	Consider cholinesterase inhibitor
Multiple lacunar strokes	Stepwise neurological impairment	Focal findings, sensory or motor loss	CT or MRI brain	Antiplatelet treatment, control of risk factors (e.g.- Diabetes, Hypertension, increased cholesterol)
Progressive supranuclear palsy	Early falls backwards, cognitive or behavioral changes	Gaze palsy (down more than up), axial rigidity, frontal and pyramidal signs, poor response to Levodopa	MRI Brain	Levodopa trial

Fig 2: Common causes of Parkinsonism [adapted from ref 24]

Parkinson's Disease Risk and Protective Factors

There are several different pathogenicity and morbidity risk factors for PD. Several studies on ageing, cancer prevention, and nutrition have revealed a positive correlation between dairy consumption and the incidence of PD [25]. The lengthening of the plantation period increased the incidence of Parkinson's disease (PD) in the Honolulu-Asian Ageing Research (HAAS) and Cancer Prevention and II Nutritional Research (CPS-IIN) research groups. This finding is consistent with the health of agriculture research that suggests pesticide disclosure raises the danger of acquiring Parkinson's disease (PD) [26].

Pesticides disrupt mitochondrial function and lead to oxidative stress, trauma to the brain can result in a breach in the blood-brain barrier, decreased mitochondrial activity, and the build-up of brain α -syn protein, all of which may raise the likelihood of developing Parkinson's disease (PD) in years following the injury [27]. According, to a study, in Finland, having a high BMI

(27.9 to 29.9) or weight, increases possibility of contracting Parkinson's disease (PD) [28].

Numerous studies have revealed a variety of PD preventive factors. According to longitudinal studies, alcoholics had marginally fewer chances of developing Parkinson's disease (PD) than non-drinkers, which is consistent with how alcohol affects urate levels in the body [29]. Numerous prospective studies have shown that drinking coffee lowers the risk of Parkinson's disease. Black tea's components may assist in lowering the possibility of developing Parkinson's disease (PD), while green tea's outcome may not have the same effect as black tea [30].

The risk of PD is lowered by up to 70% with longer smoking periods, and it has risen over time for those who have given up smoking [31]. Additionally, the use of antihypertensive medications, exercise, eating a balanced diet can dramatically lessen the damage and ameliorate the disorder of Parkinson's disease patients [32].

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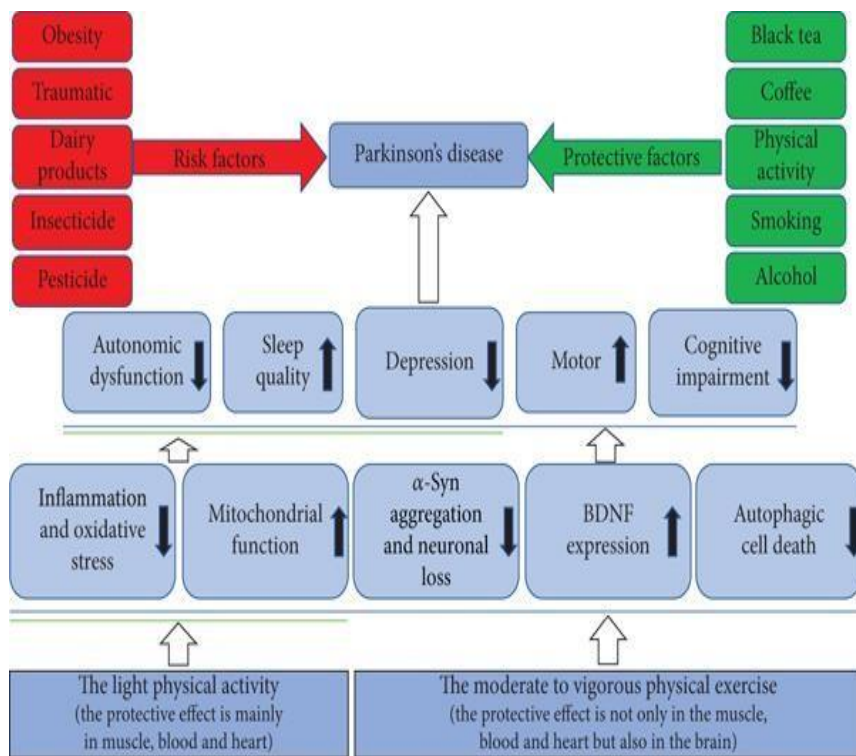


Figure 3: Representation of Parkinson's disease physical activity [Reference 33]

Research on adult and embryonic stem cells have revealed that cells have the capacity to self-renew and to generate differentiated tissues, such as dopaminergic neurons [34]. In variety of disorders these novel techniques give genuine hope for tissue replacement.

Parkinson's patients receive dopamine neurons from human stem cells in a transplant in the laboratory [35]. In the future, Parkinson's patients may have hope if a limitless supply of dopamine neurons can be successfully generated. Embryonic stem cells (undifferentiated cells collected for several scientific purposes, day-old embryos are currently being employed [36]. A large percentage of these embryos are created by in vitro fertilization procedures. Theoretically able to be modified into a component of any body tissue, researchers think they may be able to stimulate these cells to grow in place of those lost as the disease progresses [37].

Hope exists that adult stem cells, which are taken out of bone- marrow, could be applied similarly to produce outcomes [38]. Although this form of research raises fewer ethical considerations, some professionals think that using adult stemcells may be more challenging than using those from embryos [39].

In either case, there is a strong consensus among scientists that preventing them from using both types of stem cells will hamper their ability to conduct research and hinder any possible discoveries. Studies on neurotrophic factors in humans are also under consideration [40].

Conclusion and Future Direction for Research

The prevalence of morbidity and mortality rates are elevated in Parkinson's disease, one of the most prevalent neurodegenerative diseases affecting the elderly. Knowledge of symptoms of the disease, potential therapy, and long-term progression is necessary for appropriate case management. Knowing the neuropathology of Parkinson's disease and how it affects the neurological system as a whole also evolved tremendously. Neither of these remedies, however, are curative. The most important needs that need to be addressed by ongoing and future research initiatives are that PD is a condition that worsens with time, and eventually ends in severe impairment because of how severe are the treatment-resistant motor and non-motor symptoms.

The creation of a medication that slows the neurodegenerative processes unrelenting progression is the biggest Parkinson's disease has a significant unmet therapeutic need. The term "disease modification" refers to a variety of interventions, from those that aim to halt the underlying degeneration to those that replace or regenerate damaged neurons. All current efforts to create efficient disease-modifying therapies have been ineffective. Numerous explanations for these failures have been put forth, including our incomplete understanding of illness etiology and the belief that most individuals with the same clinical diagnosis will be affected by each targeted disease mechanism.

To progress Parkinson's illness disease modification, we emphasize therapies under ongoing clinical development that reveal a wide range of serious unresolved difficulties and concerns. It is still unknown if the defective molecular pathways/organelles subject to alteration emerge differently in distinct molecular subtypes of Parkinson's disease (PD) or arise sequentially across the majority of clinically affected patients. There may not be a "type of disruption" that applies to subgroups depending on unknown factors such as genetic variability and other sources of PD heterogeneity, rather than an "order of disruption" that applies to the majority of patients.

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