

## Parkinson's Disease – History, detection, and cure

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### ABSTRACT

*This paper talks about the neurodegenerative disease commonly known as Parkinson's disease, about the history of this disease and its causes, various subtypes, as well as how the diagnosis of this disease takes place. It has mainly 3 causes those being environment, genetics, or interactions. It usually happens to people above the age of 60, but there are younger cases as well. This disease causes loss of dopaminergic neurons in the brain; these neurons help in motor activities of the body, thus their loss causes loss of motor activities of the body. The dopamine-producing neurons Substantia Nigra are directly affected. The neurons degenerate due to the accumulation of Alpha's nuclein in the brain. The paper discusses how motor, non-motor and psychological aspects should be taken into account during the identification of this disease.*

**Keywords:** Parkinson's Disease, Neurodegenerative Disease, Brain Disorder, Carbidopa-Levodopa, Dopaminergic Neurons, Disease Treatment.

### INTRODUCTION

*“Parkinson's Disease (PD) is a long-term degenerative disorder of the central nervous system that mainly affects the motor system. The symptoms generally come on slowly over time.”*

(Armstrong and Okun 548). Above 10 million Parkinson cases have been recorded. Around 6 million different variations of Parkinson disease are known to mankind. It's currently the world's fastest growing brain disorder. It has become the second most common neurodegenerative disease. It is a degenerative disease which causes movement problems, prodromal features, physiological and cognitive problems. The physical problems could be (tremors, slower movements, stiffness). Prodromal features like (rapid eye movement, sleep disorders, constipation) Rehabilitative therapy and exercise complement pharmacologic treatments and cognitive problems like (anxiety, depression, cognitive decline). In Parkinson's the dopamine producing neurons of the brain are affected, they slowly decrease and number due to absence of regeneration and creation of new nerve cells This disease will only progress, it doesn't have any cure and the only way to fight it is to stop the degeneration of the nerve cells. “For all patients with Parkinson disease, treatment is symptomatic, focused on improvement in motor (eg,tremor,rigidity, bradykinesia) and nonmotor (eg, constipation, cognition, mood, sleep) signs and symptoms”. (Armstrong and Okun 548)

This disease can be diagnosed through MRI (Magnetic Resonance Imaging) after we have released a blue dye in the brain that helps us to detect Parkinson's presence. There are many rehabilitative therapy and exercises that complement pharmacologic treatments. The main medicines given in parkinson are levodopa which help in kick starting the patients recovery.

“Parkinson's disease is the world's fastest growing brain disorder, and exposure to environmental toxicants is the principal reason. In this paper, we consider alternative, but unsatisfactory, explanations for its rise, including improved diagnostic skills, aging populations, and genetic causes” (Dorsey and Bloem 451)

### HISTORY OF PARKINSON'S DISEASE

This disease has been around since ancient times but James Parkinson was the first person to write about Parkinson's disease. “James Parkinson, who was an English surgeon, apothecary, geologist, paleontology and political activist, published his thin monograph titled An Essay on the Shaking Palsy exactly 200 years ago, in 1817, and this account represents the first description of Parkinson disease (PD) as a neurological disorder.” (Serge Przedborski 251)

“In the mid-1800s, Jean-Martin Charcot was particularly influential in refining and expanding this early description and in disseminating information internationally about Parkinson's disease. He separated Parkinson's disease from multiple sclerosis and other disorders characterized by tremor, and he recognized cases that later would likely be classified among the Parkinsonism-plus syndromes”. (Goetz 1) Him and James Parkinson were the first few people to bring this disease to light but way before James Parkinson's old Indian scriptures dating back to 1000 BC as well as some Chinese texts had already described Parkinson's disease.

“Ancient texts allude to PD-like clinical features, but the first description of PD as a neurological condition (as indicated above) is credited to James Parkinson. In his 1817 monograph, James Parkinson described a handful of patients who had a singular association of tremor at rest, slowness (bradykinesia) of or, in some cases, an absence of, voluntary movements (akinesia), stooped posture and festinating gait. Beginning with Jean-Martin Charcot, approximately 50 years later, a succession of illustrious scientists contributed to the comprehensive description of the clinical range and anatomopathological basis of PD, which is now recognised as the second most common neurodegenerative disorder after Alzheimer's disease.” (Serge Przedborski 251)

“It was noted that patients having Parkinson's disease showed neurological signs as well. These observations led to the recognition of various PD-plus syndromes, such as multisystem atrophy and progressive supranuclear palsy, which, despite often initially being diagnosed as PD, are distinct conditions that have much bleaker prognoses” (Serge Przedborski 251) He also described the patients to have symptoms like tremors, slowness, stooped posture, slow speaking, etc. Parkinson disease has no set symptoms that could be used to identify it.

“Third, recent clinical descriptions of PD have revealed non-motor features that are also a part of the disease, including cognitive impairment, psychiatric symptoms, autonomic dysfunction (such as constipation), pain and fatigue. In some patients, these non-motor features can be more troublesome than the motor manifestations, and may even present years earlier” (Serge Przedborski 251)

“Early treatments of Parkinson's disease were based on empirical observation, and anticholinergic drugs were used as early as the nineteenth century. The discovery of dopaminergic deficits in Parkinson's disease and the synthetic pathway of dopamine led to the first human trials of levodopa.” (Goetz 1)

## **SUBTYPES**

“Several recognisable subtypes exist, within which some clusters of symptoms coincide. Acknowledging these subtypes is important for various reasons. The first relates to the pathophysiology, as some symptom clusters can suggest where the disease process originally started. The second reason relates to prognosis. A 2019 study on people with autopsy-confirmed Parkinson's disease identified the presence of a diffuse malignant subtype that was associated with faster progression towards reaching relevant clinical endpoints and with reduced survival. This subtype classification remains far from offering an individual prognosis in clinical practice, as the confidence intervals for the predictions remain wide. The third reason relates to possible implications for personalised treatment, which is not yet a reality in daily practice. Genetically defined subtypes are closest to delivering personalised treatment” (Bloem et al. 2286).

Parkinson's disease consists of various subtypes, the initial subtypes are based on the motor dysfunction features but now these subtypes are characterized by the help of data-driven clustering approaches.

“Individuals with a diffuse malignant subtype (9%-16% of individuals with Parkinson disease) have prominent early motor and nonmotor symptoms, poor response medication, and faster disease progression. Individuals with mild motor-predominant Parkinson disease (49%-53% of individuals with Parkinson disease) have mild symptoms, a good response to dopaminergic medications (eg, carbidopa-levodopa, dopamine agonists), and slower disease progression.

Most cases of Parkinson disease are idiopathic,” (Armstrong and Okun 548)

Parkinson disease is not easily and routinely categorized in clinical practice. However, clinicians should recognize that there are diverse presentations of Parkinson disease, and these categories may be useful for counseling individuals with Parkinson disease regarding variability in symptoms, medication responsiveness, and progression.

## **CAUSES**

Parkinson disease is an idiopathic disease meaning it doesn't have any exact reason for its cause. “When discussing the causes of Parkinson's disease, three factors are relevant: genetics, environment, and interactions thereof”. (Dorsey and Bloem) There is a relatively good understanding of causative genes, and a person's entire genome can readily be deciphered, but the assessment of the so-called environment (ie, the sum of all potentially causative and protective factors that are present in our environment) is not possible at present. Moreover, unlike a person's genetic make-up, which is largely stable, their environment is in constant flux. Environmental factors that perhaps had an effect decades ago or that accumulated over time, possibly in interaction with genetic features, are not possible to assess. Inaccessibility of the brain further constrains etiological studies. We assume there is a continuum between causes and risk factors and counteracting protective factors of different effect sizes that occur in unique constellations. Notably, factors increasing the risk for developing Parkinson's disease are not necessarily identical to those modifying the disease course, which can only be assessed in large-scale longitudinal studies (Bloem et al. 2288)

“But in the early days treatment of Parkinson's Early treatments of Parkinson's disease were based on empirical observation, and anticholinergic drugs were used as early as the nineteenth century. The discovery of dopaminergic deficits in Parkinson's disease and the synthetic pathway of dopamine led to the first human trials of levodopa.” (Goetz 1)

“Genetics Although monogenic forms comprise a minority of all Parkinson's disease, they are important for several reasons: (1) in selected cases, identifying a monogenic cause can establish a definitive diagnosis of a particular type of Parkinson's disease during life; (2) Parkinson's disease genetics can have implications for family counselling; (3) genetics have improved our understanding of Parkinson's disease pathophysiology; and (4) monogenic Parkinson's disease might be amenable to specific gene-targeted treatments, the first of which are being evaluated in trials (this is a concrete example of personalised precision medicine for people with Parkinson's disease). To prepare for trials of these gene targeted therapies for Parkinson's disease, an international effort is establishing clinical trial-ready genetic cohorts whereas a seemingly positive result might later prove to represent a rare benign variant.” (Bloem et al. 2284)

“In clinical practice, focus should be on genes that are unequivocally linked to Parkinson's disease. When suspecting a genetic form of this disease, the best clue is a young age at onset (particularly younger than 40 years). In many countries, genetic counselling is mandatory to offer; establishing the presence of monogenic Parkinson's disease can alleviate anxiety among some individuals but increase concerns for others. Importantly, a negative result does not fully exclude a genetic cause,” (Bloem et al. 2288)

“Non-genetic factors associated with an altered Parkinson's disease risk Several toxins can produce a clinical picture resembling Parkinson's disease, such as parkinsonism resulting from exposure to the neurotoxin MPTP. In addition to these direct causes, various environmental and lifestyle factors have been evaluated as contributors to the risk of Parkinson's disease. This literature is difficult to interpret: many factors have never been replicated, conflicting results exist, a plausible mechanistic explanation is often scarce, and the observed associations could have been false. One persuasive risk factor is exposure to environmental toxins such as pesticides, for which there is converging and consistent evidence. The introduction of pesticides after World War 2—which was required to feed a fast-growing world population—could partially explain the current rise of Parkinson's disease” (Bloem et al. 2289)

Pesticide, herbicide, and heavy metal exposures are linked to an increased risk of Parkinson disease in some epidemiologic studies, whereas smoking and caffeine use are associated with decreased risks.

## **PATHOPHYSIOLOGY**

“Parkinson disease is a progressive neurodegenerative disorder that is pathologically defined by degeneration of the dopaminergic neurons in the substantia nigra and development of Lewy bodies in the residual dopaminergic neurons.” (Gazewood and Richards 267)

In the human body there is a pathway connecting neurons to striatum called nigrostriatal pathway, during loss of neurons there is a formation of clumps of proteins called lewy bodies, only after the loss of 80% of neurons do the symptoms of PD occur. There are 2 pathways called direct and indirect both effecting movement, Direct pathways increase movement while indirect pathway decreases the movement after loss of dopaminergic neurons both become unstable pathways leading to tremors, stiffness, etc symptoms to arise. “Lewy bodies are found in a broad range of brain regions in patients with PD<sup>14</sup>, these spherical eosinophilic intraneuronal inclusions were originally reported in the dorsal nucleus of the vagus nerve and the substantia innominata but, notably, there was no mention of them being found in the SN.” “This model suggests that Parkinson disease starts (stages 1 and 2) in the medulla and the olfactory bulb. This early pathology is associated with symptoms occurring prior to the movement disorder onset, such as rapid eye movement sleep behavior disorder (in which individuals lose normal rapid eye movement sleep paralysis and physically act out their dreams while sleeping) and decreased smell.” “In stages 3 and 4, pathology progresses to the substantia nigra pars compacta and other midbrain and basal forebrain structures. Pathology in these areas is associated with classic Parkinson disease motor symptoms. Parkinson disease is typically diagnosed at this stage. In advanced Parkinson disease, the pathology progresses to the cerebral cortices with onset of cognitive impairment and hallucinations” (Armstrong and Okun 550)

“This recognition might ultimately yield new diagnostic avenues, because these systemic tissues are better accessible than tissue from the brain when a person is alive.” (Bloem et al. 2285)

Parkinson disease is characterized by death of dopaminergic neurons in the substantia nigra. The pathologic hallmark of Parkinson disease is the Lewy body, a neuronal inclusion consisting largely of  $\alpha$ -synuclein protein aggregation

These initial observations led some to argue that the SN was not, in fact, the key brain region involved in PD pathology, but rather that the striatum was a more plausible locus, given the observed overt anatomical damage of the striatum in some diseases associated with parkinsonism. A fierce, protracted debate ensued that was ultimately resolved by the elucidation of the dopaminergic nigrostriatal pathway. Pathologically, Parkinson’s disease is defined by the accumulation of  $\alpha$ -synuclein in Lewy bodies and Lewy neurites. This Lewy pathology is characterised by a crowded environment of membranes, including vesicular structures and dense morphic organelles, such as dysmorphic mitochondria, and high lipid content

“The initial reports of these underpinnings stated that the brains of individuals with PD showed no overt or consistent abnormalities. However, at the end of the nineteenth century, Blocq and Marinescu posited that a left-sided 5 Hz resting tremor in a 38-year-old patient was reminiscent of the symptoms of PD. They further noted that the patient’s condition could have been caused by a tuberculous granuloma of the right cerebral peduncle that impinged on the ipsilateral substantia nigra (SN). This remarkable, serendipitous observation prompted Brissaud<sup>10</sup> to suggest that the SN may be the site of the lesion in PD.” (Serge Przedborski 251)

## **DIAGNOSIS**

“Except for genetic testing in selected cases, a definitive diagnosis can only be established based on post-mortem identification of hallmark neuropathological changes in the brain.” (Armstrong and Okun 550) Due to it being an idiopathic disease it has no as such cause of getting the disease.

“Identification of so-called red flags (i.e., specific symptoms or signs that provide a relative argument against the presence of Parkinson’s disease, and that signal the possible presence of an alternative pathology, which occurs in people with a form of atypical parkinsonism) can accelerate the diagnostic process, noting that no single red flag provides definitive certainty of a specific diagnosis.” (Bloem et al. 2285)

There are no set grounds on which this disease can be diagnosed, but various signs and symptoms are motor, non-motor and psychological that should be taken into account.

The diagnosis of Parkinson disease is difficult and diagnostic error is common, particularly in the early stages.<sup>5,6</sup> A physician who rarely diagnosed Parkinson disease should consider referring a patient suspected of having it to a physician who has more experience with the disease to confirm the diagnosis.

People with Parkinson’s disease tend to get diagnosed when the disease has already reached advanced stages, as they tend to ignore early symptoms. Many motor dysfunctions are evident signs of Parkinson’s disease, such as stiffness, slowness, tremors, bradykinesia/ akinesia, and postural instability. People tend to ignore many non-motor features that also cause the disease; these early symptoms, such as constipation, sleep disorders, depression, and anxiety, should be considered. Its diagnosis depends on the cardinal features of bradykinesia, rigidity, tremors and postural instability with the effect of gradual progression of symptoms. “A new insight is that even in early disease stages, similar pathological changes can occur in multiple organs, including the skin, colon, and salivary glands, suggesting that Parkinson’s disease is a multisystem disease.” (Armstrong and Okun) “No clinical decision rules are of proven usefulness in diagnosing early disease,<sup>4</sup> although the Parkinson’s UK Brain Bank criteria improve diagnostic accuracy in patients with advanced disease.<sup>11</sup> Given the inherent uncertainty of diagnosis in early disease and the increasing diagnostic accuracy with disease progression, physicians caring for patients with Parkinson disease should periodically reevaluate the diagnosis.” (Armstrong and Okun)

“Diagnostic errors are common in daily practice. In clinical trials of early-stage Parkinson’s disease, up to 15% of people with the disease are diagnosed incorrectly; this misclassification rate is even higher among non-experts. The presence of comorbidity might complicate the diagnostic process One common comorbidity is the presence of concurrent cerebrovascular lesions, which regularly appear on brain imaging during routine diagnostic tests. These lesions can produce manifestations similar to lesions in Parkinson’s disease, such as gait disturbances, cognitive decline, or urinary incontinence” (Bloem et al. 2286)

## EARLY-STAGE DETECTIONS AND SYMPTOMS

### What has not worked in trying to identify early cases

Parkinson's is a neurodegenerative disease that progresses over time, in this disease the dopaminergic neurons present in the substantia nigra degenerate. Usually, cases of Parkinson's are idiopathic, but can also be genetic. By the time a patient receives a diagnosis, they are often in advanced stages, making it challenging to stop the degenerative effects. Therefore, it's become essential for us to identify Parkinson's disease in the early stages for successful treatment. The diagnosis of this disease is difficult and tends to have many diagnostic errors. It's rarely diagnosed in earlier stages as physicians don't tend to consider it. Till now, no proper clinical decision rules have been formed to properly diagnose Parkinson's in the early stages. "Although the Parkinson's UK Brain Bank criteria improve diagnostic accuracy in patients with advanced disease." (Armstrong and Okun 267)

Various studies have shown that in earlier clinical stages, several motor and non-motor signs emerge, which can be considered to help diagnose the early stages of Parkinson's disease. Patients usually above 50 years of age develop Parkinson's. There are some cases where people develop parkinson before 50 and this is called young onset parkinson. "Although Parkinson's disease affects both sexes, women might have several advantages over men: their incidence of the disease is lower," (Bloem et al.) "The number of years lived with disability is highest for men. However, women are disadvantaged in other ways: they have a higher risk of developing dyskinesia, and motor and non motor response fluctuations, which might result from their usually lower body weight (causing relative over-dosing). Also, women are more likely to report urinary complaints and depression" (Bloem et al.)

"Parkinson's disease is an age-related disease, with incidence and prevalence increasing steadily with age. However, the misconception that Parkinson's disease exclusively affects older people should be dismissed. The age of onset for almost 25% of affected individuals is younger than 65 years and for 5–10% is younger than 50 years. The term young-onset Parkinson's disease has been introduced when referring to affected individuals with an age of onset younger than 40 years (maybe even younger than 50 years)" (Gazewood and Richards)

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### PROGNOSIS

"Pathologic changes may be detected up to 20 years before the onset of motor symptoms and are accompanied by a clinical prodrome of nonspecific symptoms such as hyposmia, constipation, and fatigue. The disease affects approximately 1 percent of persons older than 60 years, and up to 4 per cent of those older than 80 years." (Armstrong and Okun)

Parkinson's disease occurs in over 30 different conditions, thus, we use the term Parkinsonism for diseases related to bradykinesia or akinesia. It has become one of the most common diseases.

In daily practice, Parkinson's disease is a clinical diagnosis, and is based on history taking and neurological examination. Although intended primarily for use in clinical research, following the International Parkinson and Movement Disorder Society's diagnostic criteria for Parkinson's disease can guide clinicians in establishing the diagnosis

### CONCLUSION

This research paper had taken an in-depth look into the past of Parkinson's disease and was able to conclude that this disease has been present since the BC era and was in Indian and Chinese scriptures way before it was explained by Jamer Parkinson in the 1800. The first few causes had also been properly detailed which helped to identify common factors to look for as signs of this particular disease. Parkinson's disease has many subtypes depending on the motor dysfunction and depending on the reaction to the medicine and physiotherapy this lays out the basis of the characterization. Parkinson's disease is an idiopathic disease having no set causes and can even happen to those people that don't have genetic history related to this disease, it has mainly 3 causes being environment, genetics or interactions. It usually happens to people above the age of 60 but there are younger cases as well, this disease causes loss of dopaminergic neurons in the brain, these neurons help in motor activities of the body, thus their loss cause loss of motor activities of the body, The dopamine producing neurons Substantia Nigra is directly affected. The neurons degenerate due to accumulation of Alpha's nuclein in the brain. The diagnosis of this disease is very tough and often patients are misdiagnosed. The diagnosis of Parkinson's disease is based on the person's history and physical examination, proper diagnosis of this disease can only be done after MRI, CT scans, etc thus making it very difficult to diagnose in early stages. For the treatment of Parkinson's disease, Cardiodopa- Levodopa is introduced into the brain and is the main medicine for the treatment of this disease, but it's been found that physiotherapy, exercise and rehabilitation therapy has helped way more in the healing process.

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