International Journal of Pharmacotherapy

www.ijopjournal.com

ISSN 2249 - 7765
Print ISSN 2249 - 7773

CURRENT UNDERSTANDING OF PARKINSON'S DISEASE

Shivani Pandey[1*], Babita Singh[2]*, Rajesh Verma[2], Mahdi AA[1]

[1]Department of Biochemistry, King George's Medical University, Lucknow, India.
[2]Department of Neurology, King George's Medical University, Lucknow, India.

ABSTRACT

Parkinson disease is second most common Neurological Disorders. Pub-Med query for "Parkinson disease" yields more than 2,000 articles per year each of the last 5 years. The cause is unknown, but growing evidence suggests that it may be due to a combination of environmental and genetic factors. Treatment during the early stage of Parkinson's disease has evolved, and evidence suggests that dopamine agonist mono-therapy may prevent the response fluctuations that are associated with disease progression. Surgical treatment is an option for a defined patient population. The aim of this study is to provide current update about this disease. In this review we discuss recent discoveries in the fields of current understanding as epidemiology, path-physiology, diagnosis and treatment of PD and focus on how a better understanding of disease mechanisms gained through the study that provided novel therapeutic targets.

Key words: Parkinson's disease, diagnosis, treatment, management.

INTRODUCTION

Parkinson's disease (PD or simply idiopathic Parkinsonism, primary parkinsonism or paralysis agitans) is the most common form of age-related motoric neurodegenerative disease initially described in the 1800's by James Parkinson as the 'Shaking Palsy'. Loss of the neurotransmitter dopamine was recognized as underlying the pathophysiology of the motor dysfunction [1].

Motor dysfunction disorders refer to those neurological diseases that cause disorders of movement not attributable to motor weakness or spasticity, sensory loss, or to cerebellar ataxia [2]. Movement disorders are characterized either by poverty and slowness of movement and increased tone (akinetic-rigid syndromes), or by abnormal involuntary movements (dyskinesias)—the main types of dyskinesia are tremor, chorea, myoclonus, tics, and dystonias. Most movement disorders occur with dysfunction of the subcortical brain structures comprising the basal ganglia (fig 1) [1].

A memorable acronym for the PD motor sequelae is TRAP, a mnemonic for tremor, rigidity, akinesia, and postural imbalance. Subsequently discovery of dopamine replacement therapies brought substantial symptomatic benefit to PD patients. However, these therapies do not fully treat the clinical syndrome nor do they alter the natural history of this disorder motivating clinicians and researchers to further investigate the clinical phenotype, pathophysiology and etiology of this devastating disease. Here we present our current understanding of PD epidemiology, pathology, clinical symptoms and therapeutic approaches with an emphasis on recent research.

Resources

This article reviews the current scenario of PD. The review is based on search of Medline, database & citation list of relevant publication.

Epidemiology

PD is the second most common neurodegenerative disorder after Alzheimer's disease. The etiology of PD remains obscure, although the disease symptomatology can be well controlled by levodopa, related medications and deep brain stimulation. The epidemiological features have been discussed in depth in the literature, but the methodologies used to

Corresponding Author:- **Dr. Shivani Pandey** Email: drshivani111263@gmail.com

approach the issues have varied greatly, and the results cover a wide range of factors and are generally inconclusive [3, 4] It is common in the elderly and prevalence rises from 1% in those over sixty years of age to 4% of the population over eighty years [1]. Incidence and prevalence estimates vary to a large extent—at least partly due to methodological differences between studies—but are consistently higher in men than in women. Several genes that cause familial as well as sporadic PD have been identified and familial aggregation studies support a genetic component. Despite a vast literature on lifestyle and environmental possible risk or protection factors, consistent findings are few. There is compelling evidence for protective effects of smoking and coffee, but the biologic mechanisms for these possibly causal relations are poorly understood. Prospective epidemiologic studies suggested in large cohorts of men (total: 374,003 subjects) agree in which the risk of suffering Parkinson's disease diminishes progressively as the consumption of coffee and other caffeinated beverages increases [5].

Uric acid also seems to be associated with lower PD risk. Evidence that one or several pesticides increase PD risk is suggestive but further research is needed to identify specific compounds that may play a causal role. Evidence is limited on the role of metals, other chemicals and magnetic fields [6].

The prevalence of PD is about 0.3% of the whole population in industrialized countries. The mean age of onset is around 60 years, although 5–10% of cases, classified as young onset, begin between the ages of 20 and 50 [2]. Some studies have proposed that it is more common in men than women, but others failed to detect any differences between the two sexes. The incidence of PD is between 8 and 18 per 100,000 person– years [1].

Future epidemiologic studies of PD should be large, include detailed quantifications of exposure, and collect information on environmental exposures as well as genetic polymorphisms.

Pathophysiology

The basal ganglia, a group of "brain structures" innervated by the dopaminergic system, are the most seriously affected brain areas in PD. In general, it can be said that Parkinson's disease occurs as a result of decreased levels of dopamine neuron death in the substantia nigra pars compact by 40 - 50% were accompanied by eosinophilic cytoplasmic inclusions (Lewy bodies). The function of Lewy bodies in PD pathobiology is not understood. Basal ganglia (BG) is composed of some of the core group, namely

1. Striatum (neostriatum and limbic striatum) Neostriatum consists of the putamen (Put) and caudate nucleus (NC)
2. Globus Palidus (GP)
3. Substantia Nigra (SN)
4. Subthalamic Nucleus (STN)

BG influence to muscles movement, it can be shown through participation in BG motor circuit is established between the motor cortex to the spinal cord core.

The most extreme hypotheses argue about peripheral versus central nervous system origin, intrinsic cellular oscillator versus network oscillators, and basal ganglia-based pathophysiology versus cerebellar-thalamic based pathophysiology. Recent studies support the view that parkinsonian symptoms are most likely due to abnormal synchronous oscillating neuronal activity within the basal ganglia. Peripheral factors do only play a minor role for the generation, maintenance, and modulation of PD tremor and other signs. The most likely candidates producing these neuronal oscillations are the weakly coupled neural networks of the basal ganglia-thalamo-cortical loops. However, the present evidence supports the view that the basal ganglia loops are influenced by other neuronal structures and systems and that the tuning of these loops by cerebello-thalamic mechanisms and by other modulator neurotransmitter systems entrain the abnormal synchronized oscillations [6]. Neurosurgical procedures, such as lesions or high-frequency stimulation of different parts of the loop, might resume the normal unsynchronized activity of the basal ganglia circuitry, and, therefore, ameliorate the clinical symptoms of Parkinson's disease.

There are five major pathways in the brain connecting other brain areas with the basal ganglia. These are known as the motor, oculo-motor, associative, limbic and orbito-frontal circuits, with names indicating the main projection area of each circuit. All of them are affected in PD, and their disruption explains many of the symptoms of the disease since these circuits are involved in a wide variety of functions including movement, attention and learning [7]. Scientifically, the motor circuit has been examined the most intensively. A particular conceptual model of the motor circuit and its alteration with PD has been of great influence since 1980, although some limitations have been pointed out which have led to modifications [6]. In this model, the basal ganglia normally exert a constant inhibitory influence on a wide range of motor systems, preventing them from becoming active at inappropriate times. When a decision is made to perform a particular action, inhibition is reduced for the required motor system, thereby releasing it for activation. Dopamine acts to facilitate this release of inhibition, so high levels of dopamine function tend to promote motor activity, while low levels of dopamine function, such as occur in PD, and demand greater exertions of effort for any given movement. Thus the net effect of dopamine depletion is to produce hypokinesia, an overall reduction in motor output.

Clinical features

There are four cardinal features of PD that can be rouped under the acronym TRAP: Tremor at rest, Rigidity, Akinesia (or bradykinesia) and Postural instability. In addition, flexed posture and freezing (motor blocks) have been included among classic features of parkinsonism, with PD as the most common form. Because of the diverse profiles and lifestyles of those affected by PD, motor and nonmotor impairments should be evaluated in the context of each patient's needs and goals [8]. Different rating scales are used for the evaluation of motor impairment and disability in patients with PD, but most of these scales have not been fully evaluated for validity and reliability [9, 10]. The Hoehn and Yahr scale is commonly used to compare groups of patients and to provide gross assessment of disease progression, ranging from stage 0 (no signs of disease) to stage 5 (wheelchair bound or bedridden unless assisted). The Unified Parkinson's Disease Rating scale (UPDRS) is the most well established scale for assessing disability and impairment [9, 11]. Studies making use of UPDRS to track the progression of PD suggest that the course of PD is not linear and that the rate of deterioration is variable and more rapid in the early phase of the disease and in patients with the postural instability gait difficulty (PIGD) of PD [12-14].

Other recognized motor signs and symptoms include gait and posture disturbances such as festination (rapid shuffling steps and a forward-flexed posture when walking) [15], speech and swallowing disturbances including voice disorders [16] mask-like face expression or small handwriting, although the range of possible motor problems that can appear is large [15]. Parkinson's disease can cause neuropsychiatric disturbances which can range from mild to severe. This includes disorders of speech, cognition, mood, behaviour, and thought. In addition to cognitive and motor symptoms, PD can impair other body functions. Sleep problems are a feature of the disease and can be worsened by medications. Symptoms can manifest in daytime drowsiness, disturbances in REM sleep, or insomnia [15]. Alterations in the autonomic nervous system can lead to orthostatic hypotension (low blood pressure upon standing), oily skin and excessive sweating, urinary incontinence and altered sexual function. Constipation and gastric dysmotility can be severe enough to cause discomfort and even endanger health [17]. PD is related to several eye and vision abnormalities such as decreased blink rate, dry eyes, deficient ocular pursuit (eye tracking) and saccadic movements (fast automatic movements of both eyes in the same direction), difficulties in directing gaze upward, and blurred or double vision [18]. Changes in perception may include an impaired sense of smell, sensation of pain and paresthesia (skin tingling and numbness). All of these symptoms can occur years before diagnosis of the disease [15].

Differential Diagnosis

The correct diagnosis of Parkinson's disease is important for prognostic and therapeutic reasons and is essential for clinical research. Investigations of the diagnostic accuracy for the disease and other forms of parkinsonism in community-based samples of patients taking antiparkinsonian medication confirmed a diagnosis of parkinsonism in only 74% of patients and clinically probable Parkinson's disease in 53% of patients.

The clinical findings are usually asymmetrical in PD. The clinical diagnosis may often appear straightforward & post-mortem studies have shown an alternative diagnosis in up to a quarter of patients with PD diagnosed by general neurologists. There is substantially less diagnostic error in patients diagnosed in expert movement disorder clinics [19] which strengthens the argument for early referral of patients to specialists expert in movement disorders.

A number of clinical criteria have been established. Table 1- outlines an abbreviated form of the UK Parkinson's Disease Society Brain Bank clinical diagnostic criteria.

There are a number of other clinical signs that are worth highlighting. A change of handwriting with micrographia is often an early feature as is reduced facial expression. A loss of arm swing on one side is also an early and useful diagnostic feature. A glabellar tap does not seem to be particularly sensitive or specific. A reduced sense of smell is, however, worth asking about since this may be one of the first symptoms in early PD [20]. As the disease becomes more advanced, hypophonia, drooling of saliva (from reduced swallowing) and impairment of postural reflexes may develop.

There is no definitive test for diagnosis. Historically, pathological confirmation of the hallmark Lewy body on autopsy has been considered the criterion standard for diagnosis [21]. In clinical practice, diagnosis is typically based on the presence of a combination of cardinal motor features, associated and exclusionary symptoms, and response to levodopa [22]. Although the diagnosis of PD is straightforward when patients have a classical presentation, differentiating PD from other forms of parkinsonism can be challenging early in the course of the disease, when signs and symptoms overlap with other syndromes [23]. Other Diagnostic criteria have been developed by the National Institute of Neurological Disorders and Stroke (NINDS) (Table 3) [24].

Criteria for definite PD

All criteria for probable Parkinson's are met and Histopathological confirmation of the diagnosis is obtained at autopsy.

Criteria for probable PD

At least three of the four features in group A are present and None of the features in group B is present (note: symptom duration >3 years is necessary to meet this requirement) and Substantial and sustained response to levodopa or a dopamine agonist has been documented.

Criteria for possible PD

At least two of the four features in group A are present; at least one of these is tremor or bradykinesia and either none of the features in group B is present or symptoms have been present (3 years and none of the features in group B is present and either substantial and sustained response to levodopa or a dopamine agonist has been documented or the patient has not had an adequate trial of levodopa or a dopamine agonist.

Although the diagnosis of PD is a clinical one, there are certain situations where investigations can prove useful. Computed tomography (CT) and magnetic resonance imaging (MRI) brain scans of people with PD usually appear normal [25]. These techniques are nevertheless useful to rule out other diseases that can be secondary causes of parkinsonism, such as basal ganglia tumors, vascular pathology and hydrocephalus. A specific technique of MRI, diffusion MRI, has been reported to be useful at discriminating between typical and atypical Parkinsonism, although its exact diagnostic value is still under investigation. Dopaminergic function in the basal ganglia can be measured with different Positron emission tomography (PET) and Single photon emission computerized tomography (SPECT) radiotracers, also known as Potential biomarkers. Examples are ioflupane (^{123}I) (trade name *DaTSCAN*) and iometopane (*Dopascan*) for SPECT or fludeoxyglucose (^{18}F) for PET. A pattern of reduced dopaminergic activity in the basal ganglia can aid in diagnosing PD [25]. SPECT imaging using a dopamine transporter (DAT) can be helpful in differentiating PD from a number of conditions, including essential tremor and dystonic tremor, neuroleptic-induced parkinsonism and psychogenic parkinsonism all of which demonstrate normal DAT scans. Uptake within the basal ganglia is reduced in PD.

Management Investigations

There is no cure for Parkinson's disease, but medications, surgery and multidisciplinary management can provide relief from the symptoms.

The main families of drugs useful for treating motor symptoms are levodopa (usually combined with a dopa decarboxylase inhibitor or COMT inhibitor), dopamine agonists and MAO-B inhibitors. The stage of the disease determines which group is most useful. Two stages are usually distinguished: an initial stage in which the individual with PD has already developed some disability for which he needs pharmacological treatment, and then a second stage in which an individual develops motor complications related to levodopa usage [26]. Treatment in the initial stage aims for an optimal tradeoff between good symptom control and side-effects resulting from enhancement of dopaminergic function. The start of levodopa (or L-DOPA) treatment may be delayed by using other medications such as MAO-B inhibitors and dopamine agonists, in the hope of delaying the onset of dyskinesias. In the second stage the aim is to reduce symptoms while controlling fluctuations of the response to medication. Sudden withdrawals from medication or overuse have to be managed. Treatments were based on consensus among the authors and for each type of intervention the evidence was reviewed regarding aspects of symptomatic management and – where appropriate – also regarding prevention of disease progression

Specific Treatments Reviewed Indication

- Prevention of disease progression
- Symptomatic control of parkinsonism
- Prevention of motor complications
- Control of motor complications
- Control of non-motor complications

Type of intervention

Drug treatment

- Amantadine
- Anticholinergics
- Levodopa
- MAO-B inhibitors
- COMT inhibitors
- DA agonists

Ergot-compounds

- Bromocriptine
- Cabergoline
- Dihydroergocryptine
- Lisuride
- Pergolide

Non-ergot compounds

- Apomorphine
- Piripedil
- Pramipexole
- Ropinirole

Drugs used to control autonomic dysfunction

- Hypotension
- Urinary dysfunction
- Gastrointestinal dysfunction

Drugs used to control neuropsychiatric dysfunction

- Treatment of depression
- Treatment of dementia and psychosis

Surgical treatment

- Deep brain surgery
- Neural transplantation

Physical and psychosocial treatment

- Physical therapy

- Psychosocial counseling

Speech therapy

Other drugs

Other drugs such as amantadine and anticholinergics may be useful as treatment of motor symptoms. However, the evidence supporting them lacks quality, so they are not first choice treatments [26]. In addition to motor symptoms, PD is accompanied by a diverse range of symptoms. A number of drugs have been used to treat some of these problems [27]. Examples are the use of clozapine for psychosis, cholinesterase inhibitors for dementia, and modafinil for daytime sleepiness [27, 28]. A 2010 meta-analysis found that non-steroidal anti-inflammatory drugs (apart from acetaminophen and aspirin), have been associated with at least a 15 percent (higher in long-term and regular users) reduction of incidence of the development of Parkinson's disease [29].

The nonmotor complications of this disease can be quite significant. These complications include cognitive, psychiatric, autonomic, sleep, and sensory disorders. The overall occurrence of these nonmotor complications is not easily determined given limitations in making the diagnosis as well as ascertainment bias. Nonmotor complications are problematic on their own; they also have multiple effects on the motor complications patients develop.

Nonmotor complications in PD can be summarized as follows: neuropsychiatric, cognitive impairment and dementia, psychosis, depression, anxiety, autonomic dysfunction, gastrointestinal, orthostatic hypotension, sweating, urologic, sexual dysfunction, sleep disorders, insomnia, excessive daytime sleepiness, rapid eye movement behavior disorder (RBD), and sensory disorders [30].

Sleep disorders are frequent in PD. This includes both disturbed nocturnal sleep and excessive daytime somnolence. Nocturnal sleep disturbance occurs in 60–98% of patients and correlates with disease severity and levodopa intake. RBD is a para-somnia characterized by the loss of normal skeletal muscle atonia during sleep with prominent motor activity accompanying dreaming and is increasingly recognized in patients with neurodegenerative disease, particularly the synucleinopathies. There is evidence that its development can predict cognitive impairment in PD patients without dementia.

Side effects of Parkinson's drugs

The most common reactions (which occur within the first several days of a new treatment) include nausea, vomiting, dizziness (drop in blood pressure), sleepiness and visual hallucinations.

In the last few years, levodopa and dopamine agonists in particular (ropinirole, pramipexole) have been associated with the emergence of behavioral changes such as *impulse control disorders*. These are characterized by failure to resist an impulse to perform certain actions.

Impulse control disorders include a range of behaviors such as compulsive gambling (up to 5% of treated patients) or shopping, hypersexuality, binge eating, addiction to the Internet or to other recreational activities. These activities are often pleasant in the moment, but over time may become harmful to you or to others.

Surgery and Deep Brain Stimulation (DBS)

Introduced more than 40 years ago, drug treatment effectively quells the motoric symptoms of akinesia and bradykinesia. However, many patients gradually develop levodopa-induced dyskinesias and motor fluctuations about 5–15 years after the initiation of L-dopa treatment [31]. The severity of the dyskinesias varies between patients and ongoing research efforts are focused on the development of new and more effective anti-dyskinetic medications. When medications are not enough to control symptoms, surgery and deep brain stimulation can be of use32. Studies in the past few decades have led to great improvements in surgical techniques, so that surgery is again being used in people with advanced PD for whom drug therapy is no longer sufficient. Surgery for PD can be divided in two main groups: lesional and deep brain stimulation (DBS). Target areas for DBS or lesions include the halamus, the globus pallidus or the subthalamic nucleus. Deep brain stimulation (DBS) is the most commonly used surgical treatment. Although the exact mechanism of action for DBS is not clear, it is proposed that the generated impulses suppress neural activity, which in the case of subthalamic nucleus DBS (STN-DBS), dampens the PD increased STN abnormal activity resulting in an overall improvement of tremors, rigidity and akinesias. Often DBS-treated patients are able to reduce their Ldopa dose by ~50–60% resulting in a decrease in dyskinesias and report an improved quality of life [33-36]. Unfortunately, much like L-dopa therapy, the efficacy of DBS declines as PD progresses. It involves the implantation of a medical device called a brain pacemaker, which sends electrical impulses to specific parts of the brain. DBS is recommended for people who have PD who suffer from motor fluctuations and tremor inadequately controlled by medication, or to those who are intolerant to medication, as long as they do not have severe neuropsychiatric problems [37]. Other, less common, surgical therapies involve the formation of lesions in specific subcortical areas (a technique known as pallidotomy in the case of the lesion being produced in the globus pallidus) [32]. In the final stages of the disease, palliative care is provided to

enhance quality of life [38]. Some central issues of palliative care are: care in the community while adequate care can be given there, reducing or withdrawing drug intake to reduce drug side effects, preventing pressure ulcers by management of pressure areas of inactive patients, and facilitating end-of-life decisions for the patient as well as involved friends and relatives.

Gene therapy

Gene therapy involves the use of a non-infectious virus to shuttle a gene into a part of the brain. There is no debate regarding the need for novel disease modifying PD therapies. New PD treatments are currently in clinical trials and several are centered on gene therapeutic approaches to either compensate for the loss of dopamine or to protect SNpc dopamine neurons from further degeneration with the overall goal of restoring function [39, 40]. There are several reasons for pursuing a viral vector-mediated gene therapeutic approach in the context of PD; 1) since the PD pathophysiology that subserves the motoric symptoms is largely confined to one brain region, the nigrostriatal pathway, a limited area will require treatment; 2) because of the physically restricted environment of the brain, repeated injections into the nigrostriatum are not desirable, making long-term gene expression following a single treatment appealing; 3) viral vectors are diffusible and theoretically capable of efficient transduction of the striatum; 4) genes have been identified that can either modulate the neuronal phenotype or act as neuroprotective agents; and 5) there is currently no cure for this debilitating disease. The earliest attempts at PD gene therapy utilized a variety of cell and tissue transplants including fetal and autologous adrenal medullary tissue grafts, xenografts, neurospheres, cell suspension grafts and embryonic stem cells with the overall goal of augmenting dopamine content. The gene used leads to the production of an enzyme that helps to manage PD symptoms or protects the brain from further damage [41, 42]. In 2010 there were four clinical trials using gene therapy in PD41. There have not been important adverse effects in these trials although the clinical usefulness of gene therapy is still unknown [41]. Fetal nerve cell transplantation has been met with some success as a subset of treated patients experienced palliative relief for many years. The effects of long-term fetal implants have recently been evaluated and upon autopsy several subjects displayed PD pathology in the grafted tissue suggesting that the local "disease" environment within the brain brings about "de novo" PD [43, 44]. Current PD gene therapy clinical trials employ either rAAV2 or lentivirus and are focused on three therapeutic approaches; augmentation of dopamine levels via increased neurotransmitter production, modulation of the neuronal phenotype, and neuroprotection. One approach focuses on increasing dopamine production via direct delivery of genes involved in neurotransmitter synthesis while a second method is designed to change the neuronal phenotype bypassing the need for dopamine, both approaches should the ameliorate symptoms associated with PD. These therapies are also intended to delay development of end-stage disease, an important accomplishment in a progressive age-related disorder such as PD. On the other hand, delivery of a neurotrophin gene such as glial cell-derived neurotrophic factor (GDNF) or neurturin (NTN), a GDNF-related protein, is projected to slow disease progression by enhancing neuronal survival. Gene therapy affords PD clinicians the opportunity to permanently alter dopamine production and neuronal phenotype. Even in the absence of a cure these types of therapies would represent significant therapeutic advancements.

Other treatments

Repetitive transcranial magnetic stimulation (rTMS) temporarily improves levodopa-induced dyskinesias. Its usefulness in PD is an open research topic [45], although recent studies have shown no effect by rTMS [46]. Several nutrients have been proposed as possible treatments; however there is no evidence that vitamins or food additives improve symptoms.

Prognosis

PD invariably progresses with time. The Hoehn and Yahr scale, which defines five stages of progression, is commonly used to estimate the progress of the disease. Motor symptoms, if not treated, advance aggressively in the early stages of the disease and more slowly later. Untreated, individuals are expected to lose independent ambulation after an average of eight years and be bedridden after ten years. However, it is uncommon to find untreated people nowadays. Medication has improved the prognosis of motor symptoms, while at the same time it is a new source of disability because of the undesired effects of levodopa after years of use. In people taking levodopa, the progression time of symptoms to a stage of high dependency from caregivers may be over 15 years. However, it is hard to predict what course the disease will take for a given individual [47]. Age is the best predictor of disease progression. The rate of motor decline is greater in those with less impairment at the time of diagnosis, while cognitive impairment is more frequent in those who are over 70 years of age at symptom onset [41].

Since current therapies improve motor symptoms, disability at present is mainly related to non-motor features of the disease. Nevertheless, the relationship between disease progression and disability is not linear. Disability is initially related to motor symptoms [47]. As the disease advances, disability is more related to motor symptoms that do not respond

adequately to medication, such as swallowing/speech difficulties, and gait/balance problems; and also to motor complications, which appear in up to 50% of individuals after 5 years of levodopa usage. Finally, after ten years most people with the disease have autonomic disturbances, sleep problems, mood alterations and cognitive decline. All of these symptoms, especially cognitive decline, greatly increase disability [41, 47].

Table 1. Prevalence of PD

Crude prevalence (number of cases/number of population)	Crude prevalence rate/100,000	95% CI
Parkinsonism (39/5,920)	659	452–866
PD (33/5,920)	557	367–748
Drug-induced parkinsonism (3/5,920)	51	0–108
Post-stroke parkinsonism (2/5,920)	34	0–81
Parkinsonism with dementia (1/5,920)	17	0–50
PD according to gender		
Males (21/3,066)	685	392–978
Females (12/2,854)	421	183–658
PD according to residence		
Urban (11/3,660)	301	123–478
Rural (22/2,260)	973*	567–1380
PD according to education		
Illiterate (22/1,996)	1,103**	642–1564
Literate (11/3,924)	280	115–446
Crude incidence of PD (5/5,920)	84	10–158
Crude incidence of PD in males (3/3,066)	98	0–209
Crude incidence of PD in females (2/2,854)	70	0–167

CI = Confidence interval. * $p \leq 0.001$; ** $p \leq 0.0001$.

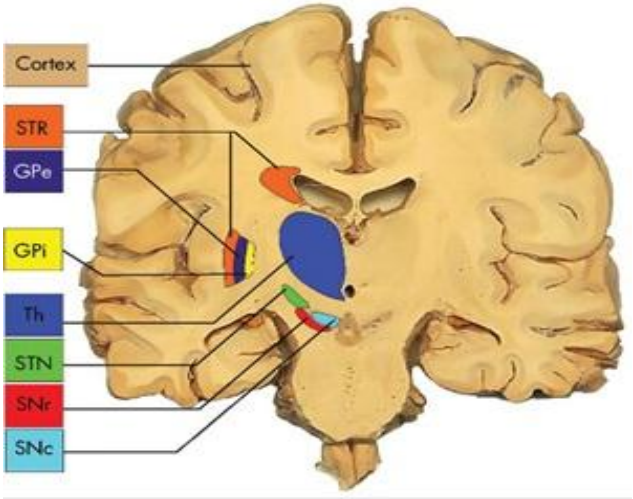
Table 2. PD–UK PDS Brain Bank diagnostic criteria

Step 1	Step 2	Step 3
Diagnosis of a parkinsonian syndrome Bradykinesia by at least one of the following:	**Exclusion criteria for PD**	**Supportive criteria for PD (three or more required for diagnosis of definite PD)**
muscular rigidity, 4–6 Hz rest tremor and postural instability not caused by primary visual, vestibular, cerebellar or proprioceptive dysfunction	**(i)** History of repeated strokes with stepwise progression of parkinsonian features (ii) History of repeated head injury (iii) History of definite encephalitis (iv) Oculogyric crises (v) Neuroleptic treatment at the onset of symptoms (vi) More than one affected relative (vii) Sustained remission (viii) Strictly unilateral features after 3 years (ix) Supranuclear gaze palsy (x) Cerebellar signs (xi) Early severe autonomic involvement (xii) Early severe dementia with disturbances of memory, language and praxis (xiii) Babinski's sign (xiv) Presence of cerebral tumour or communicating hydrocephalus on CT scan (xv) Negative response to large doses of levodopa.	(i) Unilateral onset (ii) Rest tremor present (iii) Progressive disorder (iv)Persistent asymmetry affecting side of onset most (v) Excellent response (70–100%) to levodopa (vi) Severe levodopa-induced chorea (vii) Levodopa response for 5 years or more (viii) Clinical course of 10 years or more

Table 3. Characteristic and Alternative Diagnoses of PD

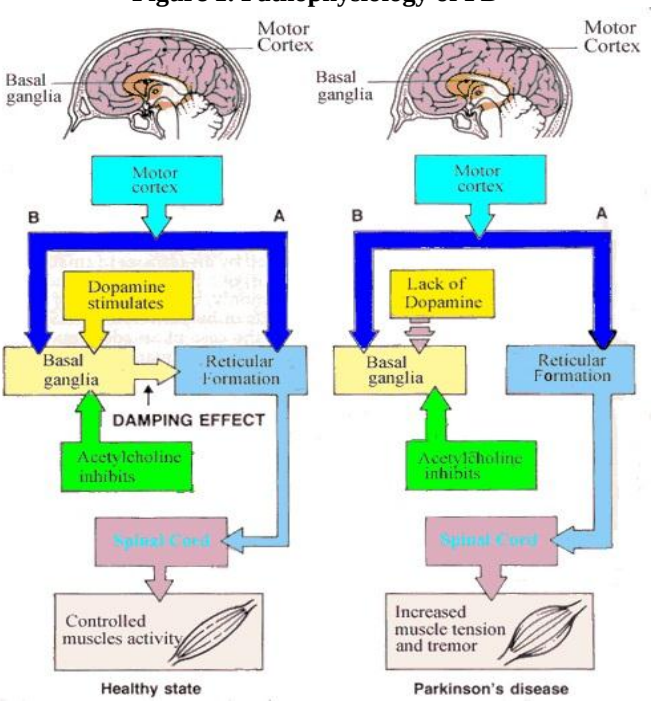
Group A features (characteristic of PD)	Group B features (suggestive of alternative diagnoses)
Resting tremor Bradykinesia Rigidity Asymmetric onset	**(i)** Features unusual early in the clinical course **(ii)** Prominent postural instability in the first 3 years after symptom onset **(iii)** Freezing phenomenon in the first 3 years **(iv)** Hallucinations unrelated to medications in the first 3 years **(v)** Dementia preceding motor symptoms or in the first year **(vi)** Supranuclear gaze palsy (other than restriction of upward gaze) or slowing of vertical saccades **(vii)** Severe, symptomatic dysautonomia unrelated to medications **(viii)** Documentation of condition known to produce parkinsonism and plausibly connected to the patient's symptoms (such as suitably located focal brain lesions or neuroleptic use within the past 6 months)

Fig 1. The basal ganglia shown in a coronal view of the brain



STR, striatum; GPe, globus pallidus pars externa; GPi, globus pallidus pars interna; Th, thalamus; STN, subthalamic nucleus; SNc, substantia nigra pars compacta; SNr, substantia nigra pars reticulata.

Figure 1. Pathophysiology of PD



CONCLUSION

Although there is no cure, there are several management options for the early treatment of PD. As the disease progresses, further treatment options are available; however, the management of late-stage symptoms remains particularly challenging and PD is a common neurodegenerative illness. Future developments in PD are likely to focus on the concept of disease modifying drugs & gene therapy which will offer neuroprotection benefit from further clinical research..

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