Medical Services

Parkinson's Diseases

Version 1 Final

Document control

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Introduction

"Parkinson's disease is characterised by impairment of movement, muscle rigidity, and tremor. It was named after an accomplished English doctor called James Parkinson (1755-1824) who after patiently observing and carefully listening to six sufferers with involuntary shaking of the body, differentiated it from other known medical causes at that time. At first he called it the shaking palsy, which later became known as Parkinson's disease. A further distinction is made between true Idiopathic Parkinson's disease when the cause of the disease is unknown, and diseases with similarities to Parkinson's such as hypothyroidism and degenerative diseases of the nervous system, which are often referred to as Parkinsonism." [1]

Description

Idiopathic Parkinson's disease (PD) is a progressive neurodegenerative condition resulting from the selective loss of the dopamine-containing neurons of the substantia nigra. The diagnosis is primarily clinical based on history and examination, although Parkinson's disease can be distinguished from other causes of Parkinsonism as it is usually asymmetrical and responsive to dopaminergic treatment. There is no consistently reliable test that can distinguish PD from other conditions and a definitive diagnosis can only be obtained at post mortem.

Parkinsonism describes a syndrome of tremor, rigidity and bradykinesia of which idiopathic Parkinson's disease is the main cause but there are also many other causes. These include drugs (7%), multiple cerebral infarction and degenerative conditions such as progressive supra-nuclear palsy (PSP) and multiple system atrophy (MSA).

Prevalence

Parkinson's Disease is estimated to affect 100–180 people per 100,000 of the population (between 6 and 11 people per 6000 of the general population in the UK) and has an annual incidence of 4–20 per 100,000. It is among the commonest causes of neurological disability in the United Kingdom.

Parkinson's disease affects about 1% of people ≥ 60 years and 0.4% of those > 40 years. The mean age at onset used to be in the late 50s but is now thought to be in the early to mid 60s. Rarely, Parkinson's disease begins in childhood or adolescence (juvenile parkinsonism).

Aetiology

The aetiology of Parkinson's disease is unknown, however, a number of factors have been implicated: [3]

The toxin MPTP causes a clinical syndrome identical to Parkinson's Disease. MPTP is converted into its active form MPP+ by monamine oxidase type B. This is taken up by the Dopamine transport systems of dopaminergic cells to cause disruption in the mitochondrial respiratory chain affecting mitochondrial complex 1 activity. Similarly impaired mitochondrial function is seen in normal Parkinson's disease suggesting that there may be a free radical insult that causes the disease. Conversely, some environmental agents appear to reduce the risk of Parkinson's disease, such as caffeine and some chemicals in cigarette smoke.

Genetic factors

About 15 % of patients have a first degree relative with Parkinson's disease, without any clear mode of inheritance. Genetic factors are thought to be of little importance in Parkinson's Disease as a result of twin studies, however, mitochondrial inheritance has to be considered and different expression of the disease in twins with later onset of the disease excluded in the first studies has meant that some authorities still believe that genetic influences are important.

Ageing

Dopaminergic neurones are affected by the ageing process declining at a rate of about 5% per decade. This rate of ageing would not account for Parkinson's disease alone but when combined with an environmental insult may explain its late age distribution.

Diagnosis

Diagnosis is clinical. Clinical criteria have been described by Gelb et al. [Appendix 1]

Presenting Features

The three key features are tremor, rigidity and bradykinesia. In most patients, the disease begins insidiously with a resting tremor (pill-rolling tremor) of one hand. The tremor is slow and coarse and maximal at rest. It lessens during movement, and is absent during sleep. It is enhanced by emotional tension or fatigue.
Usually, the hands, arms, and legs are most affected, in that order. The jaw, tongue, forehead, and eyelids may also be affected, but not the voice. Tremor may become less prominent as the disease progresses.

Rigidity is the raised resistance noted during passive joint movement, and can develop a cogwheel character when the limb is tremulous. As rigidity progresses, movement becomes slow (bradykinesia), decreased (hypokinesia), and difficult to initiate (akinesia). Bradykinesia can be the most disabling feature of PD, and may cause problems with fine motor tasks. Rigidity and hypokinesia may contribute to muscular aches and sensations of fatigue. Patients can also have postural instability, usually in later disease, which may increase their risk of falls. The characteristic gait is of reduced arm swing and slow, shuffling movements.

The face becomes mask like, with mouth open and reduced blinking.

Early on, patients may appear depressed because facial expression is lacking and movements are decreased and slowed. Speech becomes hypophonic, with characteristic monotonous, stuttering dysarthria. Hypokinesia and impaired control of distal musculature cause micrographia (writing in very small letters) and make activities of daily living increasingly difficult. [4]

Key Findings on Examination

Parkinson's disease is suspected in patients with characteristic resting tremors, decreased movement, or rigidity.

When a clinician moves a rigid joint, sudden, rhythmic jerks due to variations in the intensity of the rigidity occur, producing a ratchet-like effect (cogwheel rigidity).

Other characteristic signs (e.g. infrequent blinking, lack of facial expression, impaired postural reflexes, characteristic gait abnormalities i.e. festinant gait) help to confirm the diagnosis. Sufferers sometimes have difficulty initiating movement and then, when in motion, are prone to hurry with their upper body hunched forwards. When they try to stop they are sometimes unable to do so and hence festination continues.

Differential Diagnoses

The differential diagnosis of PD includes normal ageing, drug induced parkinsonism, essential tremor, multiple cerebral infarcts, Parkinson's plus syndromes, vascular parkinsonism, Lewy body dementia and hydrocephalus. History should include questions about head trauma, stroke, hydrocephalus, exposure to drugs and toxins, and symptoms or history of other degenerative neurological disorders. [5]

Essential tremor

A common usually hereditary or familial disorder of movement that is characterized by uncontrolled trembling of the hands and often involuntary nodding of the head and tremulousness of the voice that is exacerbated by anxiety and by activity.

Drug induced parkinsonism:

Any drug that blocks the action of dopamine is likely to cause Parkinsonism. Drugs used to treat schizophrenia and other psychotic disorders such as behaviour disturbances in people with dementia, (known as neuroleptic drugs) are probably the major cause of drug induced Parkinsonism worldwide.

As well as neuroleptics some other drugs can cause drug induced Parkinsonism. These include prochlorperazine (stemetil) and metoclopramide (Maxolon) used to treat dizziness, nausea and vomiting. It is considered that these are two of the most common causes of drug induced Parkinsonism in the elderly - something which is not always recognised.

Multiple cerebral infarcts

Multiple infarcts in the basal ganglia and subcortical white matter may present with gait abnormalities. Tremor is not often a feature. A CT or MRI scan will demonstrate extensive small vessel disease.

Hydrocephalus

An abnormal increase in the amount of cerebrospinal fluid within the cranial cavity that is accompanied by expansion of the cerebral ventricles, enlargement of the skull and especially the forehead, and atrophy of the brain.

Lewy Body Dementia

Presents with progressive Parkinsonism and early dementia. It is associated with hallucinations, behavioural disturbance and psychosis.

Trauma - 'punch drunk' syndrome

Other neurodegenerative diseases:

progressive supranuclear palsy (Steele-Richardson-Olszewski syndrome).

An uncommon neurological disorder that is of unknown aetiology, that typically occurs from late middle age onward, and that is marked by loss of voluntary vertical eye movement, muscular rigidity and dystonia of the neck and trunk, pseudobulbar paralysis, bradykinesia, and dementia.

multiple system atrophy.

Wilson's disease

A hereditary disease that is characterized by the accumulation of copper in the body (as in the liver, brain, or cornea) due to abnormal copper metabolism associated with ceruloplasmin deficiency, that is determined by an autosomal recessive gene, and that is marked especially by liver dysfunction and disease and neurologic or psychiatric symptoms.

Post encephalitic parkinsonism

encephalitis lethargica (epidemic viral encephalitis in which somnolence is marked).

Toxins:

carbon monoxide
manganese

Treatment

Pharmacological

Motor Symptoms

Treatment should be started when symptoms start to cause disability. There is no single drug of choice in the initial pharmacotherapy of early PD, although definitive treatment of early PD is with levodopa or a dopamine agonist. Dopamine agonists are a good choice in early PD and in treatment of younger patients. They are less effective than L-dopa but will control symptoms for a few years thus delaying the need for L-dopa. In the elderly, L-dopa is the first line choice as it is better tolerated. L-dopa's main problem is that patients tend to develop motor fluctuations with 'on off' effects and also develop dyskinesias. Table 1 may help to guide the reader through the following section. [2]

Table 1 Options for initial pharmacotherapy in early PD

Initial therapy for early PD	First-choice option	Symptom control	Risk of side effects	
			Motor complications	Other adverse events
Levodopa	✓	+++	↑	↑
Dopamine agonists	✓	++	↓	↑
MAO-B inhibitors	✓	+	↓	↑
Anticholinergics	✗	Lack of evidence	Lack of evidence	Lack of evidence
Beta-blockers	✗	Lack of evidence	Lack of evidence	Lack of evidence
Amantadine	✗	Lack of evidence	Lack of evidence	Lack of evidence

KEY

+++ = Good degree of symptom control

++ = Moderate degree of symptom control

+ = Limited degree of symptom control

↑ = Evidence of increased motor complications/other adverse events

↓ = Evidence of reduced motor complications/other adverse events

Levodopa

Levodopa may be used as a symptomatic treatment for people with early PD.

The dose of levodopa should be kept as low as possible to maintain good function in order to reduce the development of motor complications.

Dopamine agonists

Dopamine agonists may be used as a symptomatic treatment for people with early PD. Non ergot agonists should be used.

A dopamine agonist should be titrated to a clinically efficacious dose. If side effects prevent this, another agonist or a drug from another class should be used in its place.

Monoamine oxidase B inhibitors

MAO-B inhibitors may be used as a symptomatic treatment for people with early PD.

Beta – blockers

Beta – blockers (Beta-adrenergic antagonists) may be used in the symptomatic treatment of selected people with postural tremor in PD, but should not be drugs of first choice. These are not generally used at all nowadays.

Amantadine

Amantadine may be used as a treatment for people with early PD but should not be a drug of first choice.

Anticholinergics

Anticholinergics may be used as a symptomatic treatment typically in young people with early PD and severe tremor, but should not be drugs of first choice due to limited efficacy and the propensity to cause neuropsychiatric side effects.

Most people with PD will develop, with time, motor complications and will eventually require levodopa therapy. Adjuvant drugs to take alongside levodopa have been developed with the aim of reducing these motor complications and improving quality of life.

There is no single drug of choice in the pharmacotherapy of later PD. Table 2 may help to guide the reader through the following section.

Table 2 Options for adjuvant pharmacotherapy in later PD

Adjuvant therapy for later PD	First-choice option	Symptom control	Risk of side effects	
			Motor complications	Other adverse events
Dopamine agonists	✓	++	↓	↑
COMT inhibitors	✓	++	↓	↑
MAO-B inhibitors	✓	++	↓	↑
Amantadine	✗	NS	↓	↑
Apomorphine	✗	+	↓	↑

KEY

+++ = Good degree of symptom control

++ = Moderate degree of symptom control

+ = Limited degree of symptom control

↑ = Evidence of increased motor complications/other adverse events

↓ = Evidence of reduced motor complications/other adverse events

NS = Non-significant result

Dopamine agonists

Dopamine agonists may be used to reduce motor fluctuations in people with later PD.

A dopamine agonist should be titrated to a clinically efficacious dose. If side effects prevent this, then another agonist or a drug from another class should be used in its place.

Catechol-O-methyl transferase inhibitors(Entacapone, Tolcapone)

Catechol-O-methyl transferase (COMT) inhibitors work by lengthening the half life of circulating L-dopa thus helping prevent the phenomenon of end of dose 'wearing off'. It is used to reduce motor fluctuations in people with later PD.

People with later PD may require the addition of entacapone and triple combination preparations of levodopa, carbidopa and entacapone are available in a range of dosages to facilitate this.

Tolcapone should only be used after entacapone has failed in people with later PD due to lack of efficacy or side effects.

Monoamine oxidase B inhibitors

MAO-B inhibitors may be used to reduce motor fluctuations in people with later PD.

Amantadine

Amantadine may be used to reduce dyskinesia in people with later PD.

Apomorphine
Intermittent apomorphine injections may be used to reduce “off” time in people with PD with severe motor complications.

Continuous subcutaneous infusions of apomorphine may be used to reduce “off” time and dyskinesia in people with PD with severe motor complications.

Non Motor Symptoms

As a result of autonomic dysfunction, patients on anti-parkinsonian drugs can have problems with constipation, urinary symptoms and postural hypotension. To aid constipation they should consume a high-fiber diet. Dietary supplements (e.g. psyllium) and stimulant laxatives (e.g. bisacodyl 10 to 20 mg orally once/day) can help.

Clinicians should be aware of dopamine dysregulation syndrome, an uncommon disorder in which dopaminergic medication misuse is associated with abnormal behaviours, including hypersexuality, pathological gambling and stereotypic motor acts. This syndrome may be difficult to manage.

Physical

Maximizing activity is a goal. Patients should perform daily activities to the maximum extent possible. If they cannot, a regular exercise program or physical therapy may help condition them physically and teach them adaptive strategies. To this end the National Institute for Health and Clinical Evidence (NICE) [2] has identified a number of key priorities including:

Physiotherapy

Physiotherapy should be available for people with PD. Particular consideration should be given to:

- gait re-education, improvement of balance and flexibility
- enhancement of aerobic capacity
- improvement of movement initiation
- improvement of functional independence, including mobility and activities of daily living
- provision of advice regarding safety in the home environment

- Coping with postural hypotension may be aided by avoiding rapid changes of posture, large meals, excessive alcohol, warm temperatures and excessive straining.

Occupational Therapy

Occupational therapy should be available with the particular intention of:

- maintenance of work and family rôles, employment, home care and leisure activities
- improvement and maintenance of transfers and mobility
- improvement of personal self-care activities, such as eating, drinking, washing and dressing
- environmental issues to improve safety and motor function
- cognitive assessment and appropriate intervention.

Speech and Language Therapy

Speech and language therapy should be available for:

- improvement of vocal loudness and pitch range, including speech therapy programmes
- teaching strategies to optimise speech intelligibility
- ensuring an effective means of communication is maintained throughout the course of the disease, including use of assistive technologies
- review and management to support the safety and efficiency of swallowing and to minimise the risk of aspiration.

The Parkinson's Disease Society www.parkinsons.org.uk is the leading charity dedicated to supporting all people with PD, their families, friends and carers.

Surgical

Currently three surgical options are available for PD.
These are SubThalamic Nucleus stimulation (STN), Globus Pallidus interna stimulation (GPi) and Thalamic stimulation.

STN and GPi have to date shown no difference in efficacy or safety and the indications for either are the same:

- have motor complications that are refractory to best medical treatment,
- are biologically fit with no clinically significant active comorbidity,
- are levodopa responsive
- have no clinically significant active mental health problems, for example, depression or dementia.

Bilateral stimulation of the subthalamic nucleus is associated with significant improvement in motor function and reduction of antiparkinsonian medications in the first 12 months after surgery. [6]

GPi is rarely performed in the United Kingdom at present though it is sometimes undertaken when STN is not possible.

Thalamic deep brain stimulation may be considered as an option in people with PD who predominantly have severe disabling tremor and where STN stimulation cannot be performed. [2]

Prognosis

Parkinson's disease is a progressive disorder which starts with mild unilateral involvement and progresses to complete dependency. It is usually staged in five stages; [3]

- Stage I Unilateral involvement only
- Stage II Bilateral involvement without impairment of balance
- Stage III Impairment of balance and functional restriction
- Stage IV Fully-developed disease retaining ability to walk and stand unassisted but otherwise markedly incapacitated
- Stage V Bed-bound or wheelchair bound unless aided

Untreated, the disorder progresses to total disability, often accompanied by general deterioration of all brain functions, and may lead to an early death.

Treated, the disorder impairs people in varying ways. Most people respond to some extent to medications. The extent of symptom relief, and how long this control of symptoms lasts, is highly variable. The side effects of medications may be severe.

Main Disabling Effects

Patients have difficulty starting to walk, turning, and stopping. The posture becomes stooped.

The gait becomes shuffling with short steps, and the arms are held flexed to the waist and do not swing with the stride.

There is a tendency to fall forward (propulsion) or backward (retropulsion) known as postural instability. This relates to loss of the involuntary movements people automatically make to maintain their balance when standing. Impairment of postural reflexes causes poor balance and may increase the risk of falls.

Dementia and depression are common. Dementia develops in about 40% of patients, and depression may affect nearly half of all patients. Depression is associated with lower cognition, history of depression, and a higher Parkinson's Disease Rating Scale score. [7] [Appendix 2]

PD patients with major depression have a significantly faster decline in activities of daily living and cognitive functions, and a faster progression along the stages of the illness as compared to non-depressed PD patients. Depression should be treated with SSRIs as tricyclics may exacerbate postural hypotension. There are very few useful drug trials of antidepressant use in PD.

Some patients do experience hallucinations, usually visual. These can be a feature of Lewy body dementia but also a side effect of dopamine agonist therapy. However the Parkinson's Disease Society reports that most people do not find them threatening or distressing and are aware that the images or sounds are not real and are able to cope with them.

Patients may have orthostatic hypotension, constipation, or urinary hesitancy. Some patients have difficulty swallowing and are at risk of aspiration.

Patients cannot perform rapidly alternating movements.

Sensation and strength are usually normal. Reflexes are normal but may be difficult to elicit because of marked tremor or rigidity.

Seborrheic dermatitis is common.

Parkinson's disease rating scale (PDRS) of Webster et al. [9] [Appendix 2] is the most widely used for the evaluation of clinical impairment in PD. A simpler test for the impact on activities of daily living using 5 items (Handipark) was proposed in 2003 but has not yet been verified for general use. [10]

Appendix A - Clinical Criteria of Gelb et al for the Diagnosis of Idiopathic Parkinson's Disease

Gelb et al used clinical features to identify patients with idiopathic Parkinson's disease. These can help accurately classify symptomatic patients. The authors are from the University of Michigan and the National Institute of Neurological Disorders and Stroke.

Clinical features of Parkinson's disease:
(1) resting tremor
(2) rigidity
(3) asymmetric onset
(4) bradykinesia

Features suggesting an alternative diagnosis:

(1) dementia preceding motor symptoms

(2) dementia in first year after symptom onset

(3) prominent postural instability in the first 3 years after symptom onset

(4) freezing phenomenon in the first 3 years after symptom onset

(5) supranuclear gaze palsy (other than restriction of upward gaze)

(6) slowing of vertical saccades (rapid small movements in both eyes that occur when changing the point of fixation)

(7) severe, symptomatic dysautonomia unrelated to medications

(8) presence of located focal brain lesion that can produce parkinsonian symptoms

(9) drug capable of causing Parkinson's disease taken within the past 6 months

Criteria for definite Parkinson's disease - both of the following:

(1) meets criteria for possible Parkinson's disease (below)

(2) histologic evidence of Parkinson's disease found on brain examination at autopsy

Criteria for probable Parkinson's disease - all 3 of the following:

(1) 3 or all 4 of the clinical features of Parkinson's disease

(2) no features present indicating an alternative diagnosis (items #3 and #4 require symptoms for at least 3 years)

(3) substantial and sustained response to levodopa or dopamine agonist

Criteria for possible Parkinson's disease - all 3 of the following:

(1) 2 or more of the 4 clinical features of Parkinson's disease

(2) either no features for an alternative diagnosis are present after 3 years OR none of the features are present to date if disease duration is less than 3 years

(3) either the patient has a substantial and sustained response to levodopa or a dopamine agonist OR the patient has not had an adequate clinical trial (viz, NOT adequate clinical trial of medication with no or inadequate or nonsustained response).

References:

Gelb DJ, Oliver E, Gilman S. Diagnostic criteria for Parkinson's disease. Arch Neurology. 1999; 56: 33-39.

Appendix B - The Parkinson's Disease Rating Scale (PDRS) of Webster et al

Webster developed a rating scale for patients with Parkinsons disease based on 10 clinical findings. The scale indicates the severity of disease and the clinical impairment. Changes in the scale over time can reflect changes due to disease progression or therapeutic interventions. The author is from the University of Minnesota.

Parameters:

(1) bradykinesia of hands (including handwriting)

(2) rigidity

(3) posture

(4) upper extremity swing

(5) gait

(6) tremor

(7) facies

(8) seborrhea

(9) speech

(10) self-care

Parameter	Finding	Points
bradykinesia of hands	no involvement	0
	detectable slowing of the supination-pronation rate; beginning difficulty in handling tools, buttoning clothes, and with handwriting	1
	moderate slowing of the supination-pronation rate in one or both sides; moderate impairment of hand function; handwriting is greatly impaired, micrographia present	2
	severe slowing of the supination-pronation rate; unable to write or button clothes; marked difficulty in handling utensils	3

rigidity	non-detectable	0
	detectable rigidity in neck and shoulders; activation phenomenon is present; one or both arms show mild, negative, resting rigidity	1
	moderate rigidity in neck and shoulders; resting rigidity is present if patient is not on medications	2
	severe rigidity in neck and shoulders; resting rigidity cannot be reversed by medication	3
posture	normal posture; head flexed forward less than 4 inches	0
	beginning poker spine; head flexed forward more than 5 inches	1
	beginning arm flexion; head flexed forward up to 6 inches; one or both arms raised but still below waist	2
	onset of simian posture; head flexed forward more than 6 inches; one or both hands elevated above the waist; sharp flexion of hands, beginning interphalangeal extension; beginning flexion of knees	3
upper extremity swing	swings both arms well	0
	one arm definitely decreased in amount of swing	1
	one arm fails to swing	2
	both arms fail to swing	3
gait	steps out well with 18-30 inch stride; turns about effortlessly	0
	gait shortened to 12-18 inch stride; beginning to strike one heel; turn around time slowing; requires several steps	1
	stride moderately shortened to 6-12 inches; both heels beginning to strike floor forcefully	2
	onset of shuffling gait; steps less than 3 inches; occasional stuttering-type or blocking gait; walks on toes; turns around very slowly	3

tremor	no detectable tremor found	0
	less than 1 inch of peak-to-peak tremor movement observed in limbs or head at rest, or in either hand while walking or during the finger-to-nose testing	1
	maximum tremor envelope fails to exceed 4 inches; tremor is severe but not constant and patient retains some control of hands	2
	tremor envelope exceeds 4 inches; tremor is constant and severe; patient cannot get free of tremor while awake unless it is a pure cerebellar type; writing and feeding self are impossible	3
facies	normal; full animation; no stare	0
	detectable immobility; mouth remains closed; beginning features of anxiety or depression	1
	moderate immobility; emotion breaks through at markedly increased threshold; lips parted some of the time; moderate appearance of anxiety or depression; drooling may be present	2
	frozen facies; mouth opens >= 0.25 inches; drooling may be severe	3
seborrhea	none	0
	increased perspiration, secretions remain thin	1
	obvious oiliness present and secretion much thicker	2
	marked seborrhea; entire face and head covered by thick secretion	3
speech	clear, loud, resonant, easily understood	0
	beginning of hoarseness, with loss of inflection and resonance; good volume and still easily understood	1
	moderate hoarseness and weakness; constant monotone, unvaried pitch; beginning of dysarthria, hesitance, stuttering, difficult to understand.	2

	marked harshness and weakness; very difficult to hear and to understand	3
self-care	no impairment	0
	still provides full self-care, but rate of dressing definitely impeded; able to live alone and may be employable	1
	requires help in certain critical areas; very slow in performing most activities but manages by taking much time	2
	continuously disabled; unable to dress, feed self or walk alone	3

Parkinsons disease rating scale =

= SUM(points for all 10 parameters)

Interpretation:

• minimum score: 0

• maximum score: 30

• The higher the score the greater the disease severity and disability.

Scale	Disability
1 − 10	early illness
11 - 20	moderate
21 − 30	severe or advanced

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