

Parkinson's Disease - diagnosis and current management options

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Highlights / Hoogtepunte

- How to make the clinical diagnosis of Parkinson's disease.
- What should be considered in the differential diagnosis of Parkinson's disease?
- Treatment options: non-pharmacological, pharmacological and neuro-surgical.
- Hoe om die kliniese diagnose te maak van Parkinson se siekte.
- Watter ander sietetoestrande moet oorweeg word in die differensiële diagnose van Parkinson se siekte?
- Behandelingsopsies: nie-farmakologies, farmakologies en neurochirurgies.

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INTRODUCTION

Parkinson's disease (PD) is a common neurodegenerative disorder, with an insidious onset and slow progression over time. The causes of PD are still largely unknown but genetic factors¹ as well as environmental factor are thought to be important. There is no diagnostic test available for making the diagnosis of PD. Knowledge of the clinical signs and skill in detecting them are therefore of extreme importance to make an early and accurate diagnosis of this condition. PD affects more than one in a thousand people in the United States and occurs in as many as 1 in 100 persons over the age of 60.²

There is no cure yet for PD, but it is possible to manage both the early phase of the disease, as well as the later complications effectively.

DIAGNOSIS OF PARKINSON'S DISEASE

Symptoms

No specific diagnostic test exists for the diagnosis of PD. Diagnosis is based upon the clinician's ability to elicit both the history of symptoms, as well as finding the clinical signs that form the disease complex of PD. The clinical features that make up this disease

complex of Parkinson's syndrome consists of resting and postural tremor, rigidity (muscle stiffness), bradykinesia (slowness of movement) and postural instability (imbalance).

Since initial findings are often difficult to interpret, the false diagnosis of PD can occur in as many as 30% of patients. In order to increase the accuracy of diagnosis, it is been suggested that before the definite diagnosis of PD can be made, bradykinesia and at least one of the three other features (namely rigidity, resting tremor or postural instability) should be present in the patient.

Tremor

The tremor of PD possesses a number of characteristic features. It is more evident at rest, typically decreases with the use of the affected limb and is usually unilateral in the early stages of the disease. Tremor is found in 70% of patients suffering from PD³.

Rigidity

Patients subjectively experience rigidity as muscle stiffness or soreness. They can complain of generalized aches and pains⁴. This is often not very helpful, since this is a very non-specific symptom and can be associated with many other conditions.

Bradykinesia

Bradykinesia is often the clinical feature that causes patients suffering from early PD to seek help. It can be very stressful for the patient, because this could often be interpreted as depression or a lack of interest in the immediate surroundings.

Bradykinesias may manifest in many different ways and the following symptoms are often helpful in detecting its presence:

1. Change in handwriting: if handwriting becomes very small (micrographia), this is very suggestive of PD.
2. Shuffling gait: initially this can be subtle, where the patient would drag a foot slightly or have a reduction in or absence of swinging of the arms when walking (loss of associated movement) or, just walking at a much slower rate.
3. Slowness with simple motor tasks: dressing, washing, using utensils to eat and turning over in bed.
4. Loss of facial expression (poker-face) and soft voice (hypophonia).

Postural Instability

This refers to problems with balance and a tendency to fall. This is usually a finding that occurs in a much later stage of PD and can present itself as a

tendency to stumble or have frequent falls.

Clinical signs

In the neurological examination of the patient, the cardinal features of PD should be sought.

Tremor

The tremor found in PD is typically a slow (4-6 Hz), alternating tremor⁵, the so-called pill-roll phenomenon. It is a resting tremor, i.e. a tremor that occurs when the limb in which the tremor is present is at rest, and often improves when a conscious action is undertaken. It usually begins on one side and remains more severe in the initially affected limb. Facial and neck tremors can occur, but not voice tremor, as seen in essential tremor. It is best to examine tremor at rest, held against gravity and while in action.

Bradykinesia

Bradykinesia is slowness of movement and is often the most distressing part of PD. This is often observed by watching the patient walk into the examination room. Typically the patient will have difficulty getting out of the chair and has a decreased swinging of the arms. Dragging of a leg, small shuffling steps and a stooped posture can be present. Another finding indicating bradykinesia is that of a decreased eye-blink response and stark facial expression, or so-called "poker face".

To test for bradykinesia the patient is usually asked to perform rapid alternating movements, such as tapping the forefinger against the thumb, opening and closing the hands or pronating and supinating the arms. The patient can be asked to write his name a couple of times to test for micrographia. A similar test for the lower leg consists of tapping the heel against the floor several times, or asking the patient to get up out of a chair.

Observe for asymmetry, because this is a strong indicator of idiopathic PD.

Rigidity

The examiner feels rigidity by moving a limb around a fixed point, for instance flexing and extending an elbow, or rotating the wrist. Rigidity can have a ratchet-like quality and this is termed

"cog-wheeling". Alternatively, where the rigidity is a constant tightness, the term "leadpipe" is sometimes used.

Postural Instability

Postural instability is tested with the patient standing up and the physician standing behind the patient. After a warning to the patient, a quick pull on the shoulders is performed to see whether the patient would lose balance. It is important that the examiner should be able to support the patient, should he fall. However, this clinical finding is usually absent in early PD.

DIFFERENTIAL DIAGNOSIS

Essential tremor

Essential tremor is the condition most commonly misdiagnosed as PD. It occurs during action, is rapid and consists of co-contraction of muscles. There is often a family history of tremor in patients suffering from essential tremor.⁶

Drug side-effects

A number of medications can induce a clinical syndrome reminiscent of PD. It is important to review all medication taken by the patient and to withdraw drugs known to cause PD like symptoms before making the final diagnosis of PD. True drug induced Parkinsonism per definition is reversible. However, some symptoms can persist for extended periods of weeks to months after termination of the medication. Clinical improvement should be seen after stopping these medications. Medication that can cause PD-like symptoms include:

- Antipsychotics (e.g. haloperidol, chlorpromazine)
- Antiemetics (e.g. metocloperamide, chlorpromazine)
- Dopamine depleting drugs (reserpine)

Parkinson Plus syndromes

The most significant issue to be addressed in the differential diagnosis is whether the patient suffers from primary PD, or some other Parkinsonian syndrome⁷. These are often very difficult to distinguish from one another, but certain features should raise the

suspicion that the patient suffers from a Parkinsonian syndrome rather than idiopathic PD. These distinguishing features can include the following:

- Symmetrical onset and persistent symmetrical features of illness.
- Very rapid progression over a short period of time.
- Failure to respond to levodopa therapy or dopamine agonist treatment
- Early onset of dementia.

Other causes of Parkinson's like syndromes

1. Depression
2. Severe arthritis
3. Normal pressure hydrocephalus
4. Physical changes associated with advanced age.
5. Brain tumors
6. Head trauma
7. Infections (post-viral encephalitis)

TREATMENT OPTIONS

The ideal treatment should give brain protection and possibly reversal of the degenerative process that causes the disease. This is not yet possible and currently, the major emphasis of treatment is on the control of symptoms and prevention or treatment of complications caused by some of the symptomatic medications used. Treatment can be roughly divided into non-pharmacological, pharmacological and neurosurgical approaches.

Non-pharmacological treatment

Physical and Occupational Therapy

Patients with difficulty in balance and walking should be referred for physical and occupational therapy. The focus here would be on making the patient's environment as safe as possible, and includes walking aids.

Speech Therapy

In instances where there is severe abnormality with speech and swallowing problems, evaluation and treatment by a speech therapist can be of value.

Dietary Advice

A well-balanced diet with a high fibre content, as well as sufficient hydration, is advised for all patients.

Exercise and Complementary Therapies

Limited, but safe forms of exercise, including walking in patients who can manage, is encouraged in all patients suffering from this condition.

Pharmacological treatment

Neuroprotection

Many compounds have been shown to prevent neurodegeneration in laboratory conditions. These compounds include antioxidants, anti-inflammatory drugs, neurotrophic drugs and co-enzyme Q10⁸. Earlier suggestions that selegiline (Eldepryl®) has neuroprotective effects is currently being disputed. This drug does delay the need for levodopa and may be a reasonable choice in the early stages of treating PD. Currently, there is insufficient evidence to recommend any specific treatment for neuroprotection⁹.

Symptomatic Control

The strategy here is either to replace dopamine, or to simulate dopaminergic receptors by virtue of synthetic compounds.

Levodopa

Levodopa (Carbilef®, Madopar® and Sinemet®) is still the most effective symptomatic agent¹⁰. The only limitation for the use of this drug are the dopa-related complications that follow long-term treatment and the emergence of dopa-resistant symptoms, such as gait and balance problems, freezing and dysphagia.

Patients on levodopa therapy, in advanced Parkinson's disease, can develop motor abnormalities related to medication. This can present in many forms- the most problematic being motor fluctuations and dyskinesias.

- Motor fluctuations refer to the situation where drug effectivity waxes and wanes a short time after intake- this can have an insidious onset with subsequent "freezing" episodes and falls.
- Dyskinesias are abnormal movements – usually choreiform, often seen at peak dose of medication.

These are, however, late complications only seen in patients that have been on

levodopa therapy for a number of years.

Levodopa is available in several formulations, which include regular tablets and slow release formulations. Controlled release tablets (Madopar HBS® and Sinemet CR®) ensure relatively constant plasma levels for a longer period¹¹, and are therefore preferred in patients with mild to moderate PD who do not have dopa-induced dyskinesias.

In more advanced disease, gastrointestinal motility becomes variable and the absorption of medication erratic. In more severe cases, it is reasonable to switch to regular tablets rather than a controlled-release formulation. Controlled-release drugs are considerably more expensive than the regular formulation, with the only advantage being the possible delay in the development of motor complications after long-term therapy.

Catechol-O-Methyl Transferase inhibitors (COMT inhibitors)

COMT inhibitors reduce metabolism of levodopa¹². Two of these drugs are available, namely entacapone and entacapone (Tasmar® and Comtan®). Tasmar® has been associated with fatal liver damage in some patients and the usefulness, therefore, has been limited¹³. These drugs can be useful in the management of dyskinesias in patients with advanced disease, but are expensive and should be reserved for patients with severe dopamine-related side effects. This drug is not a first-line form of therapy.

Dopamine agonists

Many dopamine agonists have emerged over the years. This started with bromocriptine and pergolide, with the recent addition of pramipexole and ropinerole in South Africa. None of these drugs stimulate all the dopamine receptors in the same way as levodopa. Most stimulate the D-2 type receptors primarily. These antagonists are, however, effective in all stages of PD and especially as monotherapy in patients with mild to moderate disease¹⁴.

Use of this type of medication delays the need for levodopa and thereby the development of dyskinesias and motor fluctuations. No direct comparative studies between the dopamine agonists

exists, and therefore the decision as to which dopamine agonist is suitable for a patient should be made considering factors such as doctor and patient preference, financial implications and availability of medication. It is a reasonable practice to start treating patients suffering from PD with dopamine agonists as a first-line therapy to relieve the symptoms of the condition and also to possibly prevent long-term motor complications. Side-effects include hallucinations, orthostatic hypotension and sleep attacks¹³.

Apomorphine is also a dopamine agonist stimulating both the D-1 and D-2 receptor types. This drug, however, needs to be injected and has a very short half-life, with very marked peripheral side-effects⁴. It is available in South Africa, but only on a special motivation and should be reserved for selected patients.

Non-dopaminergic approaches

These medications have their effect outside the dopamine system and include drugs such as amantadine (Symmetrel®) and anticholinergics (Artane® and Akineton®). These drugs can sometimes be useful in the treatment of tremor and, possibly dyskinesias (amantadine). The effects of these drugs are limited and the side-effect profile often unwanted, therefore the use of these drugs in the majority of patients are limited¹³.

Surgical therapies

The two most widely used procedures are *pallidotomy* (production of lesions in the globus pallidus for the treatment of movement disorders) and deep brain stimulation. Neurosurgery is reserved for patients with severe motor fluctuations or dyskinesias and can only be performed in specialized units¹⁵.

Initiating treatment

Treatment can often be delayed until the symptoms cause functional impairment. If there is any uncertainty about the diagnosis, refer for specialist opinion. In mild to moderate PD with normal cognition, a dopamine agonist is the appropriate first-line therapy. If the patient's symptoms are inadequately controlled, replace the dopamine agonist with levodopa, or add low dose

levodopa to the treatment regimen. In the more severe illness and in older patients (>80 years), particularly in the presence of dementia, levodopa is preferred. Other forms of treatment should be reserved for special situations.

CONCLUSION

Parkinson's disease is a common neurodegenerative disorder causing significant disability. Effective treatment is available and can improve quality of life significantly. Knowledge of the signs and symptoms of this condition will lead to early recognition of this condition that with, in turn, lead to appropriate therapy. □

Please refer to the CPD questionnaire on page 53.

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