Parkinson’s disease: an overview of diagnosis and ongoing management.

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ABSTRACT

Parkinson’s disease is a chronic neurodegenerative disorder with a myriad of motor and non-motor symptoms. Its management is essentially palliative, and it can extend to three to four decades. Device-assisted therapy including deep brain stimulation, apomorphine pump, and levodopa gel intestinal infusion, have significantly improved management of advanced Parkinson’s disease. Non-motor symptoms, including neuropsychiatric, gastrointestinal, urogenital and sleep-related symptoms can predate Parkinson’s disease diagnosis with a decade or two, and they represent a major concern to the patients and their care providers alike.

Key words: Parkinson’s disease, levodopa, dopamine agonists, apomorphine, deep brain stimulation, non-motor symptoms, DaTscan.

INTRODUCTION

Parkinson’s disease is the second most prevalent neurodegenerative disease worldwide(1). Despite all the advances in neurosciences, its diagnosis remains clinical. It was described initially, two hundred years ago, by James Parkinson in his seminal paper “An essay on the shaking palsy.”(2) This review article summarizes the essential knowledge needed by general neurologists and other healthcare providers looking after patients with Parkinson’s disease.

Pathology of idiopathic Parkinson’s disease:

The dominant pathology of idiopathic Parkinson’s disease(PD) is primarily a loss of dopamine-producing cells in the substantia nigra in the midbrain, followed by degeneration of nigrostriatal pathway, depriving basal ganglia of dopamine required to facilitate all motor activities(3).

The current theory explaining PD pathology was put forward by Braak et al., suggests that pathology starts in the gut, then utilizing the vagus nerve, it ascends to the olfactory bulb and vagal motor nucleus at the caudal medulla.
oblongata, progressing up the brainstem and diencephalon to the cortex (4-7). It is estimated that more than 50% of the nigrostriatal dopamine-producing neurons have degenerated before the first motor symptom appears (8, 9).

Diagnosis of PD:

PD diagnosis relies on the UK Parkinson’s disease Society Brain Bank criteria (10). To diagnose Parkinson’s disease, the patient must satisfy diagnostic criteria for parkinsonism first. Parkinsonism is diagnosed when bradykinesia is present, plus any of the other core features, muscular rigidity, resting tremor or postural instability. Then, the patient must fulfill other supportive criteria listed in Table 1 (10).

Table 1: UK Parkinson’s Disease Society Brain Bank clinical diagnostic criteria. (10)

<table>
<thead>
<tr>
<th>Step 1: Diagnosis of Parkinsonian syndrome</th>
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<tbody>
<tr>
<td>* Bradykinesia (slowness of initiation of voluntary movement with progressive reduction in speed and amplitude of repetitive actions)</td>
</tr>
<tr>
<td>* And at least one of the following:</td>
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<tr>
<td>Muscular rigidity</td>
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<td>4-6 Hz rest tremor</td>
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<td>Postural instability not caused by primary visual, vestibular, cerebellar, or proprioceptive dysfunction.</td>
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<tr>
<th>Step 2: Exclusion criteria for Parkinson's disease</th>
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<tr>
<td>* History of repeated strokes with stepwise progression of parkinsonian features</td>
</tr>
<tr>
<td>* History of repeated head injury</td>
</tr>
<tr>
<td>* History of definite encephalitis</td>
</tr>
<tr>
<td>* Oculogyric crises</td>
</tr>
<tr>
<td>* Neuroleptic treatment at onset of symptoms</td>
</tr>
<tr>
<td>* More than one affected relative</td>
</tr>
<tr>
<td>* Sustained remission</td>
</tr>
<tr>
<td>* Strictly unilateral features after 3 years</td>
</tr>
<tr>
<td>* Supranuclear gaze palsy</td>
</tr>
<tr>
<td>* Cerebellar signs</td>
</tr>
<tr>
<td>* Early severe autonomic involvement</td>
</tr>
<tr>
<td>* Early severe dementia with disturbances of memory, language, and praxis</td>
</tr>
<tr>
<td>* Babinski sign</td>
</tr>
<tr>
<td>* Presence of cerebraltumor or communicating hydrocephalus on CT scan</td>
</tr>
<tr>
<td>* Negativeresponse to large doses of levodopa (if malabsorption excluded)</td>
</tr>
<tr>
<td>* MPTP exposure</td>
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<tr>
<th>Step 3: Supportive prospective positive criteria for Parkinson's disease</th>
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<tr>
<td>(Three or more required for diagnosis of definite Parkinson's disease)</td>
</tr>
<tr>
<td>* Unilateral onset</td>
</tr>
<tr>
<td>* Rest tremor present</td>
</tr>
<tr>
<td>* Progressive disorder</td>
</tr>
<tr>
<td>* Persistent asymmetry affecting side of onset.</td>
</tr>
<tr>
<td>* Excellent response (70-100%) to levodopa</td>
</tr>
<tr>
<td>* Severe levodopa-induced chorea</td>
</tr>
<tr>
<td>* Levodopa response for 5 years or more</td>
</tr>
<tr>
<td>* Clinical course of 10 years or more</td>
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Movement Disorders Society (MDS) has published its version of Parkinson's disease diagnostic criteria (11). In its core, the UK Parkinson’s Society Brain Bank criteria remain essential. Comparing to the UK Brain Bank criteria,
MDS Clinical Diagnostic Criteria for Parkinson’s Disease incorporated more red flags and exclusion criteria aimed at ruling out other parkinsonian syndromes, like multiple system atrophy (MSA) and corticobasal ganglionic degeneration, as well as non-motor features of Parkinson’s disease. MDS criteria are no longer require postural instability to diagnose Parkinsonism, as it represents a red flag, if seen early.

DaTscan, a dopamineactive transporter (DAT) single photon emission computerized tomography (SPECT) imaging modality. It helps to sort out parkinsonian syndromes (idiopathic PD, Progressive Supranuclear Palsy (PSP), MSA) characterized by a dopamine deficiency, from secondary parkinsonism (e.g., drug-induced, vascular or psychogenic)(12, 13).

Since the diagnosis of PD is purely clinical, it is delayed by an average of one year(14). Even in the movement disorders specialists’ hands, the accuracy of clinical diagnosis in PD, when compared with postmortem diagnosis, ranges from 80% in early stages to 84% after refining the diagnosis in subsequent follow-up(15). This accuracy has not improved over the last twenty-five years(15). The diagnosis should be revisited at least once a year, and clinical or historical indicators of Parkinson-plus disorders are sought(16).

Once the diagnosis is clinically established, deciding on whether to start treatment, or on what agent to use, is individualized. Disability and patient’s preference play a major role in such decision(17).

Drug therapy of PD motor symptoms:

For an early to moderate stage of PD, available symptomatic therapies include anticholinergics, amantadine, MAO-B inhibitors (selegiline and rasagiline), dopamine agonists and levodopa.

The main decision point is when to start a dopaminergic drug, and whether that agent is a dopamine agonist or levodopa.

Levodopa introduction in 1967 has revolutionized PD therapeutics and has changed the landscape of PD treatment (18, 19). Delaying levodopa, when patients need it, to avoid loss of effect, has no clinical evidence to support it. All patients lose effect with time, and they will require increasingly larger doses to obtain a satisfactory motor response (20).

When compared to dopamine agonists, levodopa is more effective, and is less associated with impulse control disorders (ICDs) than dopamine agonists. ICDs include compulsive shopping, gambling, hyper sexuality, punding, dopamine dysregulation syndrome and compulsive eating (21-23).

In its 2002 guidelines on initiating treatment in PD, which was reviewed in 2006, the American Academy of Neurology suggested there was not enough evidence to use dopamine agonists first. It concluded it is reasonable to initiate treatment with levodopa, dopamine agonist or an MAO-B inhibitor(24, 25).

When Parkinson’s disease advances, side effects of dopaminergic therapy start accumulating. The commonest of these side effects is a loss of efficacy before the next dose is scheduled (wearing off), levodopa-induced dyskinesia, and ICDs.

Long-term use of levodopa leads to motor fluctuations and dyskinesia. Development of dyskinesia is related to levodopa dose and duration. The higher the levodopa dose and the longer the duration it is used, the more likelihood dyskinesias develop(26). Reasons for levodopa-induced dyskinesia include short half-life of levodopa, the need to dose it frequently, coupled with degeneration of the nigrostriatal neurons that store and slowly release dopamine. Delayed gastric emptying is thought to play a major role in dose failure, as well as decrease the efficacy of oral therapy(27).

Device-assisted therapy:
Continuous levodopa delivery has emerged as a practical means to treat motor fluctuations and oral levodopa-induced dyskinesias. Levodopa intestinal gel infusion (LIGI), is an infusion of levodopa gel via an external pump, through a percutaneous gastrojejunal tube(28, 29).

Apomorphine, a rapid onset D1/D2 dopamine agonist, is used to treat freezing by subcutaneous injection. It is infused continuously via a subcutaneous route through a small pump held externally by the patient. It is effective for smoothing out motor fluctuations as well as a host of non-motor symptoms(30).

Deep brain stimulation (DBS) is a two-step neurosurgical procedure. First, an electrode is placed deep in a selected target in the brain, followed by implanting a neurostimulator in the pectoral region and connecting it to the electrode (31, 32).

LIGI, apomorphine pump and DBS are used for patients with motor fluctuations and other advanced complications of oral therapy, and are better left to specialists in tertiary care centers with enough volume and expertise. The selection of the appropriate patients and modality need careful consideration. These modalities are invasive and expensive(33).

Non-motor symptoms:

Non-motor symptoms (NMS), including constipation, rapid eye movement (REM) sleep behavior disorder (RBD), anosmia, anxiety, and depression can predate the motor symptoms with a decade or two. They were largely overshadowed by motor features, especially in early clinical trials, which were mostly geared towards motor features control. Over the last twenty years or so, NMS have been recognized as a major source of concern to patients, and grading scales have been developed and incorporated into clinical trials(34-37).

Hallucinations are common in later stages of PD(38). They start with friendly non-threatening imagery, then they become frightening. Treatment is not needed if hallucinations are non-threatening. When caregivers or patients indicate a need for treatment, eliminating culprit drugs with less motoric benefit and more hallucinating potential is the first step.

Clozapine has the most clinical evidence in treating PD associated psychosis (39-42). It is plagued by the need to monitor patients for neutropenia frequently. Quetiapine has no evidence supporting its use. Nonetheless, anecdotal reports and single patients’ experiences show it works. It has no serious side effects, and it needs no monitoring, apart from corrected QT interval (QTc)(43). Pimavanserin, a select serotonin 5-HT2A inverse agonist, could become the first-line therapy, especially after the promising results it showed in Cummings et al., study(44). Typical antipsychotics should be avoided, as they worsen PD symptoms.

Constipation can predate PD diagnosis with a decade or two(45). Gastric emptying is slowed by over 40%(27), with delayed absorption. Subsequently, oral medications become less effective. Constipation, untreated, can lead to bowel obstruction and death in PD patients(46).

Constipation is best managed by increasing hydration, fruits and vegetables in the diet. Fiber-containing agents are to be avoided, as they worsen constipation with slow gut transit time.

Polyethylene glycol (PEG) 3350, a macrogol, is an osmotic agent, that has the best clinical evidence for use in PD(47). It can be given up to 4-5 times daily when needed. The aim is to have one bowel movement per day.

Dysphagia and aspiration are frequent in advanced PD. Video fluoroscopy is the standard diagnostic procedure. It is treated first with thickened fluids and by avoiding dry crusty bread and nuts(48, 49). When advanced, enteral tube feeding is an option to allow enough calories be taken to prevent weight loss. A Cochrane review found that enteral feeding did not improve the quality of life(50).

Orthostatic hypotension (OH) presents clinically with falls upon standing. “Coat hanger pain” syndrome is classical. It presents as pain in both shoulders upon standing, disappearing when lying flat(51). To diagnose orthostatic hypotension, the patient should lie down quietly for five minutes, then take the supine blood pressure measurement.
After at least 2-3 minutes of standing up, blood pressure is measured again. If systolic blood pressure drops more than 20 mmHg from the baseline or Systolic drops below 90 mmHg, it is considered orthostatic hypotension or absolute hypotension, respectively. OH is treated by increasing fluids during day time. If that alone is not helping, midodrine in the morning and noon time is effective(52, 53).

Fludrocortisone has less evidence in the treatment of orthostatic hypotension. It causes hypokalemia, and it should be monitored(54).

Dysarthria and palilalia are difficult to treat, but hypophonia can be helped by Lee Silverman Voice Treatment (LSVT), which is essentially teaching patients how to shout (55).

Depression affects 40-50% of patients with PD(56). Tricyclic antidepressants (TCA) have the best available evidence, though anticholinergic side effects limit its use in the elderly(57). Selective serotonin reuptake inhibitors (SSRIs) were inferior when compared to TCA, but they are better tolerated and are more frequently used(58).

RBD is common among patients with Parkinson’s disease. It leads to loss of safe sleep, and to acting out dreams with subsequent injuries to the patient or the bed partner. It is treated with clonazepam, though this can lead to tolerance (59, 60).

Less responsiveness to levodopa is unavoidable; pain subsequently develops secondary to stiffness. Physiotherapy to keep the range of motion and function of the affected limbs is essential(61).

CONCLUSION

PD management along its wide spectrum remains a challenge, it is largely palliative, but not terminal care. The aim is to keep patients as active as possible, using management strategies that have the least possible interference with their daily activities. Once PD advances to a late non-responsive stage, withdrawal of medications could start, and a more holistic approach should be instituted, in collaboration with palliative care specialists.

REFERENCES


