Diagnosis and Initiation of Treatment of Parkinson Disease (2007)

Philippine Neurological Association

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Management Algorithm for Parkinson Disease

1. Parkinson disease

2. Diagnosis

3. Is there functional impairment?

4. Initiate treatment

5. Age >60
   - Initiate treatment with LEVODOPA

6. Motor complications?
   - Y
     - Add COMT
     - Add Dopamine agonists
   - N
     - Keep L-dopa

7. Age <60
   - Initiate treatment with DOPAMINE AGONIST

8. N
   - Neuroprotection

9. Age <60
   - If not enough, add L-dopa

10. N
    - Consider surgery if unacceptable control with medical treatment

11. Y
   - Initiate treatment with DOPAMINE AGONIST

12. Monitor

13. If not enough, add L-dopa

Figure 1
Parkinson Disease

Diagnosis and Initiation of Treatment of Parkinson Disease

Introduction

Parkinson disease (PD) is a neurodegenerative disorder first described in 1817 by James Parkinson as the "shaking palsy". It is the second most prevalent neurodegenerative disorder after Alzheimer's disease. The classical features include rest tremor, bradykinesia and rigidity. Postural instability is a late feature seen in advanced stages of Parkinson disease. Based on the Philippine Prevalence Studies released in 2005, the local prevalence rate of parkinsonism was 0.03%.

Parkinson disease is one of many disorders characterized by parkinsonism, which is a syndrome composed of combinations of bradykinesia, rigidity, tremor and postural instability. Parkinson disease may be classified as idiopathic parkinsonism. There are secondary causes of parkinsonism, which include drug induced parkinsonism, vascular lesions like stroke, structural causes such as tumors, infectious causes such as SSPE and post-encephalitic parkinsonism, trauma (boxers parkinsonism) and toxin induced parkinsonism.

Majority of cases of Parkinson disease occur sporadically. Typical age of onset is between 50-70 years old. There are however patients whose age of onset occur earlier. These are called Young Onset Parkinson Disease (YOPD) where the age of onset is less than 40 years old. In the past few years various genetic mutations have been identified in patients with clinically diagnosed Parkinson disease. The mutations are seen in some families with a family history of Parkinson disease or in those with Young Onset Parkinson Disease.

Diagnosis

The diagnosis of PD is made clinically, based on the presence of the core features of bradykinesia (slowing), rest tremor and rigidity (See Appendix 1). The diagnosis is usually uncomplicated when this classical triad is present. Diagnostic difficulties arise when the so-called classical features are absent.

Perhaps a common source of diagnostic confusion is related to tremor. The tremor in Parkinson disease is a rest tremor. It is present when the affected limb is at rest and absent with voluntary activity. It frequently appears when walking. Tremor in Parkinson disease is often confused with essential tremor, which is perhaps the most common movement disorder. Tremor in essential tremor is a postural and action tremor. It is absent when the involved hand is at rest but appears when the hand is elevated or involved in a voluntary activity such as writing. Another common source of confusion is when tremor is absent. About 30% of patients with Parkinson disease do not have tremor.

Bradykinesia means decreasing speed and amplitude of repetitive movements. Often patients would complain of difficulty with fine finger movements such as buttoning buttons or using small tools. Another frequent complaint is weakness of the hand or leg. However, examination would reveal that strength is normal. Bradykinesia is tested in the arms by asking the patient to perform rapid, alternating movements. For example, one can ask the patient to open and close the hands or tap the forefinger and thumb rapidly. Initially, they may perform well but the speed and amplitude of movement subsequent declines. In the legs, bradykinesia can be sought by asking the seated patient to tap the floor with the heel.

Rigidity is the increased muscle tone, that is present throughout the range of movement and does not vary with the speed of the passive movement. Patients experience rigidity as a vague ache or discomfort. In the arm this is tested by gentle wrist extension/flexion, elbow extension/flexion and forearm supination/pronation, while feeling for any increase in muscle tone. Similar movements are used in the legs while supine.

Patients with Parkinson disease may experience other symptoms. They may complain of slowing of walking, dragging of the foot and absence of arm swing on the affected side. Getting out of cars or rising from a deep sofa becomes difficult. Handwriting becomes smaller (micrographia). Relatives may notice softening of voice (hypophonia) and loss of facial expression (masked facie).

Parkinson disease is asymmetric at disease onset. Typically, patients would report the onset of tremor or slowing of movement on one side. The contralateral side is eventually affected with disease progression. However, despite the involvement of both sides, the symptoms tend to be worse on the side where the symptoms first appeared. Symmetric involvement of both sides at onset is a red flag and other causes of parkinsonism must be considered.

The list of causes of parkinsonism is extensive and includes toxins, infections of the central nervous system, structural lesions of the brain such as tumors or strokes, metabolic disorders and other neurologic disorders. In clinical practice, the physician should routinely consider two alternative diagnoses: drug-induced parkinsonism and parkinsonism-plus syndromes.

It is crucial to rule out drug-induced parkinsonism since it is reversible. However, reversal may take several weeks or months after the offending drug is stopped. In one study, drug-induced parkinsonism accounted for 20% of cases of parkinsonism. Frequent offenders include commonly used drugs such as: neuroleptic agents (haloperidol), atypical neuroleptic drugs (risperidone), calcium channel blockers (cinnarizine and flunarizine), anti-emetics (promethazine, prochlorperazine, metoclopramide), reserpine and valproic acid.

Parkinsonism-plus syndromes are uncommon neurologic
disorders where parkinsonism occurs in association with other symptoms. These symptoms include falling or dementia early in the course of the disease, poor response to levodopa, symmetry of motor symptoms, absence of tremor, and early autonomic dysfunction such as urinary or fecal incontinence, urinary retention, erectile dysfunction, and orthostatic hypotension. The presence of these symptoms should alert the physician that other diagnoses should be considered. Neurologic consultation maybe warranted.

**IS THERE FUNCTIONAL IMPAIRMENT?**

When to initiate symptomatic treatment of Parkinson disease is rather controversial. Making a diagnosis of Parkinson disease is not a reason to start treatment. Most specialists begin treatment when a patient starts to experience functional impairment. How one defines functional impairment should take in account the uniqueness of an individual. Patients progress at different rates and parkinsonian features may have different functional implications for each individual.

Several factors should be considered in determining functional impairment. One factor is whether the dominant hand or non-dominant hand is affected. A right-handed patient with involvement of the right hand will have more functional impairment than a person with the same degree of impairment in the non-dominant hand.

Employment and employability are important factors. Even minor symptoms can impair performance at work and threaten employability.

A third factor is the parkinsonian feature seen in the individual. Those with gait impairment or imbalance should be considered functionally impaired. These symptoms can lead to falls and serious injury.

Finally, the degree to which symptoms affect motor function and activities of daily living is an important determinant of functional disability. Patients should be questioned about speech, salivation, swallowing, handwriting, cutting food, handling utensils, hygiene, turning in bed, falling, walking, tremor and sensory symptoms.

**NO FUNCTIONAL IMPAIRMENT**

Pharmacologic treatment is not needed if functional impairment is not present. Nonpharmacologic interventions may be initiated during this time. As physicians we tend to concentrate on pharmacologic and surgical approaches to diseases. However, we must be aware of the importance of nonpharmacologic interventions in Parkinson disease. These include education, support services, management of emotional needs of the patient and caregiver, exercise, nutrition and physical therapy.

The issue of neuroprotection may be brought up at this time. In Parkinson disease, neuroprotection is an intervention that protects or rescues vulnerable nigral neurons and slows or stops disease progression. Vitamins E or C are frequently prescribed for their antioxidant and supposed neuroprotective benefits. Some physicians use selegiline, a MAO-B inhibitor as a putative neuroprotective therapy. It is given at a dose of 5 mg twice daily, at breakfast and lunch. Its neuroprotective benefit is believed to be due to its anti-apoptotic (programmed cell death) mechanism.

But what is the evidence? The American Academy of Neurology published a practice parameter on neuroprotective strategies and alternative therapies for Parkinson disease in 2006 (Practice Parameter: Neuroprotective Strategies and Alternative Therapies for Parkinson’s Disease, Neurology 2006; 66:976-982). In this paper, they recommended that vitamin E should not be considered as having a neuroprotective benefit. There was no evidence for long-term neuroprotection from levodopa. At the same time, there was insufficient evidence to support or refute the use of rifuzole, coenzyme Q10, pramipexole, ropinirole, rasagiline and amantadine. Finally, there was insufficient evidence to recommend selegiline for neuroprotection.

**IF FUNCTIONAL IMPAIRMENT IS PRESENT**

Pharmacologic therapy is appropriate once a patient is determined to be functionally impaired. Effective drugs for initial therapy include dopaminergic agents such as levodopa and dopamine agonists, anticholinergics, amantadine and selegiline (See table). Clinical experience has shown that the dopaminergic agents are more potent than anticholinergics, amantadine and selegiline.

**Levodopa**

Levodopa, a precursor of dopamine, is the most effective antiparkinsonian drug. It is the gold standard of treating Parkinson disease. It was in 1967 when Cotzias and colleagues demonstrated the dramatic improvement in motor symptoms in Parkinson disease with levodopa. It rapidly became the drug of choice for Parkinson disease.

Levodopa is combined with a peripheral decarboxylase inhibitor such as carbidopa or benserazide to reduce the peripheral degradation of levodopa before it reaches the brain. This prevents peripheral side effects such as nausea and vomiting and allows more of the levodopa to be available for use by the brain. Levodopa/carbidopa combined with a catechol o-methyltransferase inhibitor, entacapone, is another preparation intended to extend the action of levodopa. Dietary amino acids coming from foods rich in protein interfere with the absorption of levodopa, which is therefore best taken on an empty stomach.

Patients on levodopa for five to ten years developed complications such as levodopa-induced dyskinesias. These are involuntary movements that are choreic or dance-like in character, occur in response to chronic levodopa use.
Patients with Young Onset Parkinson disease (onset <40 years old) are particularly susceptible to the development of dyskinesias. On the other hand, dyskinesias are less likely to occur in those whose symptoms appear after the age of 70.

**Dopamine Agonists**

Dopamine agonists directly activate dopamine receptors. Currently available dopamine agonists include piribedil and pramipexole. While they are slightly less expensive than levodopa, dopamine agonists are alternative first line drugs for Parkinson disease. Dopamine agonists, unlike levodopa, are not affected by dietary amino acids. Thus, they can be taken with or after meals. An important potential advantage of dopamine agonists is that, their use is associated with a reduced risk of dyskinesias and motor fluctuation. The current recommendation for piribedil is as adjunct to levodopa. There is an ongoing study assessing piribedil for monotherapy.

**Deep Brain Stimulation for Parkinson Disease**

The conclusion on the recent reviews of DBS for Parkinson disease has been efficacious and clinically useful as symptomatic adjunct to levodopa. The potential patients need to undergo rigid screening procedure prior to the DBS.

Hallucinations and psychosis are more common with dopamine agonists than with levodopa and are particularly prone to occur in the elderly or in patients with dementia. Dopamine agonists are therefore best avoided in these groups of patients.

**Anticholinergics, amantadine and selegiline**

The other pharmacologic agents such as anticholinergics, amantadine and selegiline generally provide inadequate symptomatic treatment when used alone. Anticholinergics such as biperiden are useful for bothersome tremors unresponsive to other medications. They are contraindicated in patients with dementia and in general it is better to avoid them in the elderly.

Whether to begin treatment of Parkinson disease with levodopa or dopamine agonists is as controversial as when to initiate treatment. To address this, the American Academy of Neurology published a practice parameter on the initiation of treatment of Parkinson disease in the journal Neurology in 2002. (Practice Parameter: Initiation of treatment of Parkinson’s Disease, An Evidence Based Review, Neurology 2002; 58:11-17).

Among the results of this evidence based review was that for patients requiring initiation of symptomatic therapy, either levodopa or a dopamine agonist could be used. Both levodopa and dopamine agonists are effective in ameliorating motor and disability in patients with Parkinson disease. However, levodopa provides superior motor benefit but is associated with a higher risk of dyskinesia. The use of dopamine agonists results in fewer motor complications (including dyskinesias) but is associated with more frequent adverse events (such as hallucinations and somnolence than levodopa).

The age of the patient may be used as a guide to assist the physician in choosing between levodopa or a dopamine agonist.

For patients, 60 years old or younger who need symptomatic treatment, dopamine agonists provide adequate antiparkinsonian benefit. At the same time, they are less sensitive to adverse effects from dopamine agonists. Using dopamine agonist initially also provides a “levodopa sparring” benefit. Starting and maintaining patients on dopamine agonists spare them from complications related to chronic use of levodopa. This is especially important for those with Young Onset Parkinson’s Disease. This group of patients is extremely sensitive to the development of levodopa-induced dyskinesia.

For older patients (>60 years old), levodopa would be the better choice. Older patients are more sensitive to adverse effects from dopamine agonist. As mentioned earlier, patients with older ages of onset are less likely to develop levodopa induced motor complications such as dyskinesias.

**Appendix 1**

**Diagnosis of Parkinson Disease**


1. Presence of at least two of the three cardinal features of parkinsonism:
   - tremor
   - rigidity
   - bradykinesia

2. Presence of at least two of the following:
   - marked response to levodopa
   - asymmetry of signs
   - asymmetry at onset

3. Evidence of disease progression
4. Absence of clinical features of alternative diagnosis
5. Absence of etiology known to cause similar features

**References:**


Table - Initial Therapy for Parkinson Disease

*Antiparkinsonian drugs are started at low doses and increased slowly to avoid adverse effects. Slow withdrawal after chronic treatment is prudent to avoid worsening of parkinsonism.

<table>
<thead>
<tr>
<th>Drug Type</th>
<th>Initial Dose</th>
<th>Usual Dose</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Levodopa plus carbidopa</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sinemet 25/100 (25 mg carbidopa, 100 mg levodopa, immediate release)</td>
<td>½ tablet 3x daily</td>
<td>1 to 2 tablets 3x daily</td>
<td>At initiation: anorexia, nausea, vomiting, dizziness, hypotension; Long term use: motor fluctuations, dyskinesias, confusion, hallucinations</td>
</tr>
<tr>
<td>Sinemet CR tablet (50 mg carbidopa, 200 mg levodopa, controlled released)</td>
<td>1 tablet 3x daily</td>
<td>same as immediate release tablet</td>
<td></td>
</tr>
<tr>
<td>Tidomet 25/250 (25 mg carbidopa, 250 mg levodopa, immediate release)</td>
<td>¼ tablet 3x daily</td>
<td>½ tablet 3x daily</td>
<td>same as above</td>
</tr>
<tr>
<td><strong>Levodopa plus benserazide</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Madopar 250 (200 mg levodopa, 50 mg benserazide)</td>
<td>¼ tablet 3x daily</td>
<td>½ tablet 3x daily</td>
<td>same as above</td>
</tr>
<tr>
<td>Madopar HBS 125 mg/cap</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Levodopa plus carbidopa plus entacapone</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stalev 50 (50 mg levodopa, 12.5 mg carbidopa, 200 mg entacapone)</td>
<td>1 tablet 3x daily</td>
<td>Same as Sinemet &amp; Tidomet plus diarrhea and discoloration of urine</td>
<td></td>
</tr>
<tr>
<td>100 mg; 150 mg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Dopamine Agonist</strong></td>
<td></td>
<td></td>
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<tr>
<td>Pramipexole</td>
<td></td>
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<tr>
<td>Sifrol 250 mcg, 1 mg tablets</td>
<td>0.125 mg 3x daily</td>
<td>0.5-1.5 mg 3x daily</td>
<td>Nausea, vomiting, hypotension, excessive daytime sleepiness, confusion and hallucinations</td>
</tr>
<tr>
<td><strong>Piribedil</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trivastal 50 mg tablets</td>
<td>1 tablet 3x a day</td>
<td>1 to 2 tablets 3x daily, up to a total of 5 tabs a day</td>
<td>Same as for pramipexole</td>
</tr>
<tr>
<td><strong>Anticholinergic</strong></td>
<td></td>
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</tr>
<tr>
<td>Biperiden (Akineton) 2 mg</td>
<td>¼ tablet once a day</td>
<td>¼ to ½ tablet 2-3x daily</td>
<td>Impaired memory, confusion, constipation, blurred vision, urinary retention, dry eyes, dry mouth and angle-closure glaucoma</td>
</tr>
<tr>
<td><strong>Amantadine</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PK-Merz 100 mg tablet</td>
<td>100 mg once a day</td>
<td>100 mg 2-3x a day</td>
<td>Dizziness, insomnia, nervousness, livedo reticularis, hallucinations, confusion</td>
</tr>
</tbody>
</table>

**Other Medications**

**Anti-emetic** Nausea or vomiting is a frequent adverse reaction during initiation of treatment with levodopa or dopamine agonist. Starting at a low dose and increasing the dosage slowly should prevent most side effects. If patients are unable to tolerate medication despite a low starting dose, an anti-emetic such as domperidone, can be used. Other anti-emetics should be avoided.

**Domperidone** (Motilum) 10 mg tablet 1 tablet, 30 minutes prior to the dose of levodopa or dopamine agonist