Parkinson Disease

Parkinson disease (PD) is a chronic, progressive movement disorder resulting from loss of dopamine from the nigrostriatal tracts in the brain, and is characterized by rigidity, bradykinesia, postural disturbances, and tremor. The age at onset of PD is variable, usually between 50 and 80 years, with a mean onset of 55 years. The symptoms of PD are progressive, and within 10 to 20 years, significant immobility results for most patients.

Etiology

The etiology of PD is poorly understood. Most evidence suggests it is multifactorial, and attributable to a complex interplay between age-related changes in brain, underlying genetic risks, and environmental triggers.

Pathophysiology

Parkinson's disease is a degenerative process involving the dopaminergic neurons in the substantia nigra (the area of the basal ganglia that produces and stores the neurotransmitter dopamine). This area plays an important role in the extrapyramidal system, which controls posture and coordination of voluntary motor movements. The loss of dopamine-producing neurons in the substantia nigra results in an imbalance between dopamine, an inhibitory neurotransmitter, and the excitatory neurotransmitter acetylcholine. This leads to an excess of excitatory acetylcholine at the synapse, and consequent rigidity, tremors, and bradykinesia. Other nondopaminergic neurons may be affected, possibly contributing to depression and the other non-motor symptoms associated with this disease.

CLINICAL SIGNS AND SYMPTOMS:

PD develops insidiously and progresses slowly. Patients with PD display both motor (bradykinesia, tremor, rigidity and postural instability) and non-motor symptoms. The non-motor symptoms may precede the motor symptoms.

(1) Motor Symptoms of PD:

1-Tremor motion in the hands is often described as "**pill rolling**," since the fingers and thumbs move in opposition as though a small object was being rolled between them.

2-Bradykinesia is a slowing of movement. Slowness of movement characterized by a slow, shuffling gait and lack of arm swing. Movement becomes increasingly impaired and can make turning in bed, rising from a low chair, and even walking increasingly difficult.

3-Postural instability is the primary cause of falls associated with PD. Signs include flexion at the knees, hips, and waist and walking on the balls of the feet.

4-Rigidity is an increase of muscle tone that is elicited when the examiner moves the patient's limbs, neck, or trunk. Rigidity of the face and trunk is often observable as a lack of facial expression (**masked facies)**. The masking of facial expression may be misinterpreted as apathy, or depression.

(2) Non-Motor Symptoms of PD: Sleep disturbances (insomnia), Autonomic symptoms (drooling, constipation, sexual dysfunction, urinary problems, sweating, orthostatic hypotension, dysphagia), Psychological symptoms (anxiety, psychosis, cognitive impairment, depression).

Diagnosis

The diagnosis is made clinically, as there is no diagnostic test for Parkinson's disease. Definite PD is diagnosed when there is at least two of the following: resting tremor, rigidity, bradykinesia, and a positive response to antiparkinson medication. Other diagnostic tests: neuroimaging to exclude other causes of PD and medication history: should be obtained to rule out drug-induced Parkinsonism.

Treatment

Once the patient is diagnosed with PD, the focus should be on improving the symptoms and maintaining an active and positive lifestyle. There is currently no cure for PD. The treatment of PD is categorized into: Lifestyle changes (nutrition, and exercise),

pharmacologic intervention, primarily with drugs that enhance dopamine concentrations and surgical intervention.

The current approach to treatment is to delay medication therapy until the symptoms begin to interfere with the patient's ability to function or impact their quality of life. Treatment needs change over the course of the disease. Medications are adjusted throughout the course of the disease, in order to maintain the best control of symptoms and avoid major side effects.

Nonpharmacologic Therapy:

1- Exercise and good **nutritional support** can be beneficial at the earlier stages to improve mobility, and enhance well-being and mood.

2-Speech therapy may be helpful, and **psychological support** is often necessary in dealing with depression and other related problems.

Pharmacologic Treatment:

The primary objective of drug therapy is to enhance dopaminergic activity within the damaged areas of the basal ganglia.

A-Levodopa and Carbidopa/Levodopa

Levodopa is a metabolic precursor of dopamine. It restores dopaminergic neurotransmission in the corpus striatum by enhancing the synthesis of dopamine in the surviving neurons of the substantia nigra. In patients with early disease, the number of residual dopaminergic neurons in the substantia nigra (typically about 20 percent of normal) is adequate for conversion of levodopa to dopamine. Thus, in new patients, the therapeutic response to levodopa is consistent, and the patient rarely complains that the drug effects "wear off". Unfortunately, with time, the number of neurons decreases, and fewer cells are capable of taking up exogenously administered levodopa and converting it to dopamine for subsequent storage and release. Consequently, motor control fluctuation develops.

1. Mechanism of action:

a. Levodopa: Because parkinsonism results from insufficient dopamine in specific regions of the brain, attempts have been made to replenish the dopamine deficiency. Large doses of levodopa are required, because much of the drug is decarboxylated to dopamine in the periphery, resulting in side effects that include nausea, vomiting, cardiac arrhythmias, and hypotension.

b. Carbidopa: Carbidopa, a dopa decarboxylase inhibitor, diminishes the metabolism of levodopa in the gastrointestinal tract and peripheral tissues, thereby increasing the availability of levodopa to the CNS. The addition of carbidopa lowers the dose of levodopa needed by four- to fivefold and, consequently, decreases the severity of the side effects arising from peripherally formed dopamine.

2. Actions: Levodopa decreases the rigidity, tremors, and other symptoms of parkinsonism.

3. Absorption and metabolism: The drug is absorbed rapidly from the small intestine (when empty of food). Levodopa has an extremely short half-life (1 to 2 hours), which causes fluctuations in plasma concentration. This may produce fluctuations in motor response, which generally correlate with the plasma concentrations of levodopa, or perhaps give rise to the more troublesome “on-off” phenomenon. Ingestion of meals, particularly if high in protein, interferes with the transport of levodopa into the CNS. Large, neutral amino acids (for example, leucine and isoleucine) compete with levodopa for absorption from the gut and for transport across the blood-brain barrier. Thus, levodopa should be taken on an empty stomach, typically 45 minutes before a meal.

Adverse effects:

a. Peripheral effects: Anorexia, nausea, and vomiting occur because of stimulation of the chemoreceptor trigger zone of the medulla. Tachycardia and ventricular extrasystoles result from dopaminergic action on the heart. Hypotension may also develop.

b. CNS effects: Visual and auditory hallucinations and abnormal involuntary movements (dyskinesias) may occur. Levodopa can also cause mood changes, depression, psychosis, and anxiety.

6. Interactions:

- The vitamin pyridoxine (B6) increases the peripheral breakdown of levodopa and diminishes its effectiveness.
- Antipsychotic drugs are generally contraindicated in parkinsonian patients. However low doses of certain "atypical" antipsychotic agents are sometimes used to treat levodopa-induced psychiatric symptoms.

Ultimately, all PD patients will require L-dopa. The decision whether to start L-dopa as soon as the diagnosis is made or only when symptoms compromise quality of life has generated controversy. Initially L-dopa 300 mg/day (in divided doses) combined with carbidopa often achieves adequate relief. The usual maximal dose of L-dopa is 800 to 1000 mg/day. Carbidopa/L- dopa is most widely used in a 25/100 mg tablet. For patients with difficulty swallowing, an orally disintegrating tablet is available. The immediate response to levodopa is often dramatic, but the long-term use is limited by the development of motor fluctuations. The most common of these is the wearing-off effect which occurs when patients experience recurrence of symptoms before the next dose of medication. Possible options to solve such problem include:

A-Carbidopa/L-dopa needs to be given more frequently so as to minimize daytime off episodes.

B- The addition of the COMT inhibitor entacapone or the MAO-B inhibitor rasagiline extends the action of L-dopa, and either should be considered.

C- A dopamine agonist (e.g., pramipexole, ropinirole) also can be added to a carbidopa/L-dopa regimen in an attempt to minimize the occurrence of wearing off. For acute off episodes, a subcutaneously administered short-acting dopamine agonist,

apomorphine, is available and possesses a rapid onset of effect (within 20 minutes). It is administered as needed.

Another complication of L-dopa therapy is dyskinesia which is an involuntary choreiform movements (too much movement) involving the neck, trunk, and lower/upper extremities. Dyskinesia usually is associated with peak dopamine levels (peak-dose dyskinesia). Possible options to solve such problem include:

1. The use of lower individual doses of L-dopa (with an increase in dosage frequency or addition of another agent to counteract the effects of using a lower L-dopa dose).
2. Addition of amantadine.

B-Dopamine Agonists

Drugs acting directly on postsynaptic dopamine receptors may have a beneficial effect in addition to that of levodopa. Unlike levodopa, they do not require enzymatic conversion to an active metabolite, act directly on the postsynaptic dopamine receptors, have no potentially toxic metabolites, and do not compete with other substances for active transport into the blood and across the blood-brain barrier. Moreover, drugs selectively affecting certain (but not all) dopamine receptors may have more limited adverse effects than levodopa. The ergot derivative bromocriptine and the non-ergots pramipexole, rotigotine, and ropinirole are beneficial adjuncts in patients with limited clinical response to L-dopa. They decrease the frequency of "off" periods and provide an L-dopa-sparing effect. The non-ergots are safer and are effective as monotherapy in mild-moderate PD as well as adjuncts to L-dopa. In younger patients (e.g., age <65 years) with milder disease, the initiation of a dopamine agonist is preferred. In older patients (e.g.,age >65 years) with PD, it may be more appropriate to initiate treatment with levodopa instead of a dopamine agonist.

C-Catechol-O-Methyltransferase (COMT) Inhibitors

Inhibition of dopa decarboxylase is associated with compensatory activation of other pathways of levodopa metabolism, especially catechol-O-methyl transferase (COMT), and this increase plasma levels of 3-O-methyldopa (3-OMD). Elevated levels of 3-OMD have been associated with a poor therapeutic response to levodopa. Selective COMT inhibitors such as **tolcapone** and **entacapone** also prolong the action of levodopa by diminishing its peripheral metabolism. Levodopa clearance is decreased and relative bioavailability of levodopa is thus increased.

Tolcapone and entacapone are used only in conjunction with carbidopa/L-dopa to prevent the peripheral conversion of L-dopa to dopamine. Thus, "on" time is increased by about ~1 to 2 hours. These agents significantly decrease "off" time and decrease L-dopa requirements. Tolcapone can cause hepatotoxicity. There is no evidence of hepatotoxicity from entacapone.

D-Monoamine Oxidase Type-B (MAO-B) Inhibitors

Inhibition of MAO-B is associated with reduced synaptic degradation of dopamine and prolonged dopaminergic activity. Two selective MAOB inhibitors, rasagiline and selegiline, are available for management of PD. Selegiline is a first-generation MAO-B inhibitor that blocks dopamine breakdown and can modestly extend the duration of action of L-dopa (up to 1 hour). Selegiline is metabolized to the amphetamine derivatives, which have been implicated in producing side effects such as insomnia and vivid dreaming. It is not given in the evening because excess stimulation from metabolites can cause insomnia. The orally disintegrating tablet formulation dissolves in the mouth on contact with saliva and undergoes pregastric absorption. This is an improvement over conventional selegiline because it minimizes the effect of first-pass metabolism and results in higher plasma concentrations of selegiline and reductions in the amphetamine-based metabolites. Rasagiline is a second-generation selective inhibitor of MAO-B. It is indicated as monotherapy in early disease or as adjunct therapy to levodopa in advanced disease. Rasagiline is differentiated from selegiline

primarily in that it is a more potent inhibitor of MAO-B, and it is not metabolized into amphetamine-based metabolites. When an adjunctive agent is required for managing motor fluctuations, rasagiline may provide 1 hour of extra “on” time during the day. It is considered a first-line agent (as is entacapone) for managing motor fluctuations.

E-Anticholinergic Medications

Anticholinergics **(e.g., benztropine, and trihexyphenidyl)** are effective in the treatment of parkinsonian tremor and to a lesser extent rigidity, but produce only a slight improvement in bradykinesia. They are usually given in divided doses, which are increased every two to five days until optimum benefit is achieved or until adverse effects occur. However, they are poorly tolerated by elderly patients owing to their cognitive side effects. Their use is mostly restricted to patients with tremor that is intractable to levodopa treatment.

F-Amantadine

For patients with mild signs and symptoms, amantadine monotherapy may be considered. Amantadine reduces all the symptoms of parkinsonian, usually within days after starting therapy; however, long-term use is limited in many patients by the development of tachyphylaxis within 1 to 3 months. Amantadine has been found to have antidyskinesia effects, the finding has shifted its emphasis from use as monotherapy in early disease to that of an adjunctive agent in managing levodopa-induced dyskinesias.

General approach to treat Parkinson disease:

Monotherapy usually begins with a monoamine oxidase-B (MAO-B) inhibitor, or dopamine agonist. For patients who are older, cognitively impaired, or having moderately severe functional impairment, L-dopa (e.g., carbidopa/levodopa) is preferred. With the development of motor fluctuations: addition of a COMT inhibitor should be considered to extend L-dopa duration of activity. B-Alternatively, addition of a MAO-B inhibitor or dopamine agonist should be considered. For management of L-dopa-induced peak-dose dyskinesias, the addition of amantadine should be considered.

Surgery

Deep brain stimulation involves the implantation of a high-frequency device that provides electrical stimulation of the specific areas in the brain. Deep brain stimulation is reserved for patients who have a good response to levodopa but in whom dyskinesias or response fluctuations are problematic.