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PARKINSON'S DISEASE

INTRODUCTION

Synonyms : Shaking Palsy or Paralysis Agitans

Parkinson's disease (PD) was first described in 1817 by Dr. James Parkinson, a family physician, in his historic document

"An Essay on the Shaking Palsy."

It is a neurodegenerative disease, meaning it is

caused by degeneration (dysfunction and death)

of neurons within some parts of the brain.

PD causes motor (movement) and nonmotor symptoms.

EPIDEMIOLOGY

Believed to affect approximately 1 million people in the United States; misdiagnosis of PD is common, however so, this figure is not precise.

The likelihood of developing PD increases with age. PD typically begins in the 50s or 60s, and slowly progresses with increasing age.

The average age of onset is 60 years. Onset before age 30 is rare, but upto 10% of cases begin by the age of 40.

It is estimated that approximately 1.5 % of people over the age of 60 years are likely to be affected by PD.

With increase in life expectancy (even in developing countries) it is estimated that the frequency of PD may increase four fold by the year 2040.

While no treatments have yet been shown conclusively to slow the disease, a large number of drugs are available to treat symptoms; so are several forms of surgeries and numerous nonpharmacological (non-drug) approaches.

SYMPTOMS

The cardinal motor symptoms (Classical Triad) are :

1. **Resting TREMORS(shaking in an arm or leg when it is not being moved)**
2. **Muscle RIGIDITY (stiffness), and postural instability**
3. **SLOWNESS of movements (called bradykinesia)**
4. **Symptoms typically begin on one side of the body (unilateral) and progress to include both sides**

Motor Symptoms

- Tremor (Classically 'Pill Rolling')
- Slowness of Motor activity (Bradykinesia)
- Rigidity and freezing in place
- Stooped, shuffling gait
- Lack of facial expression (Mask-like face)
- Decreased arm swing when walking
- Difficulty rising from a chair
- Micrographia (small handwriting)
- Slowed activities of daily living
- Postural instability
- Difficulty turning in bed

Nonmotor Symptoms

- Diminished sense of smell
- Drooling
- Low pitched voice
- Increased sweating
- Urinary frequency/urgency
- Male erectile dysfunction
- Constipation
- Painful foot cramps
- Sleep disturbance
- Depression

Oculogyric Crisis is an acute dystonic reaction, occuring with PD patients. Many medications are known to precipitate this condition

THE SUBSTANTIA NIGRA (SN) AND PD

The Substantia Nigra (literally meaning "black substance") is a small region in the brain stem. It is one of the centers that helps control movements.

Cells within the SN produce and release a chemical called 'Dopamine'. Dopamine is a vital neurotransmitter that essentially controls movement and balance.

Dopamine assists in the effective transmission of electrochemical signals from one nerve cell (neuron) to another.

Dopamine released by SN neurons lands on the surface of neurons in other brain centers, controlling their activities or "firing" and thus regulating movement.

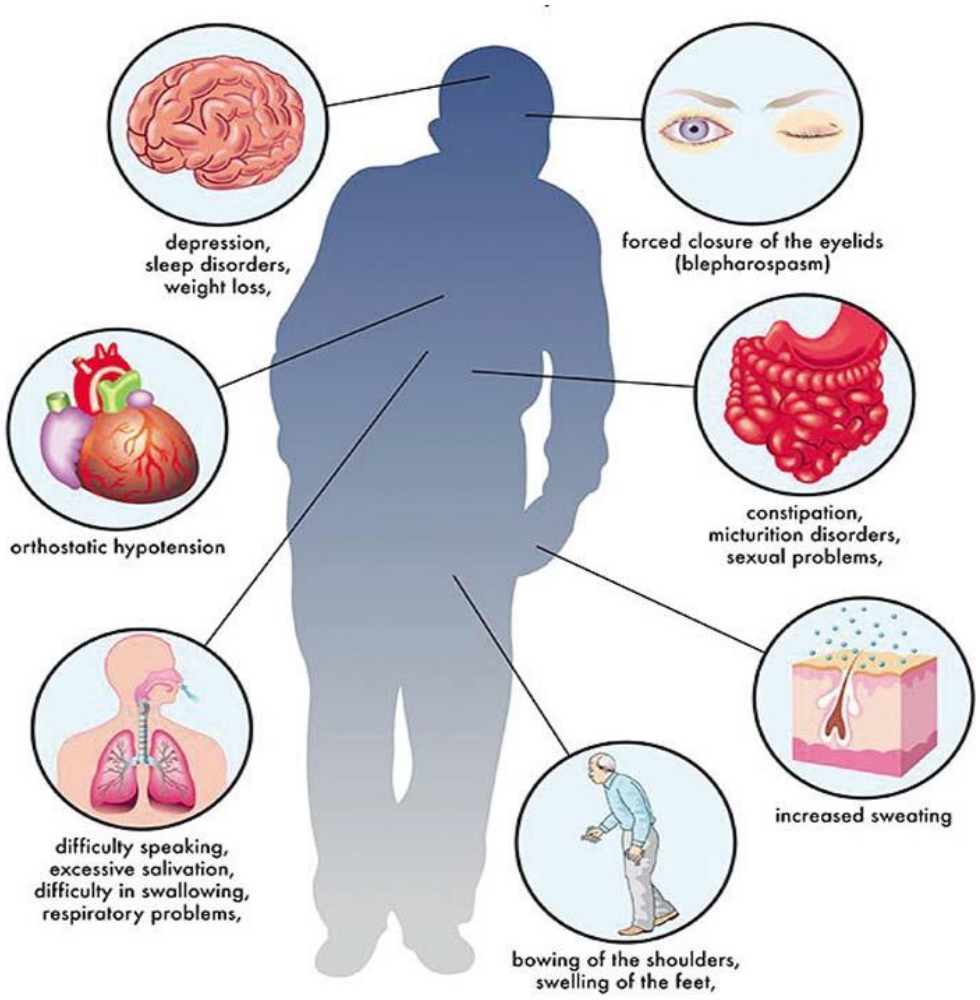
The target regions of dopamine are Caudate Nucleus and Lentiform Nucleus (=Basal Ganglia)

PD is characterised pathologically by loss of dopaminergic neurons in substantia nigra pars compacta (SNc) and presence of intracytoplasmic inclusions or lewy bodies. When this occurs, neurons elsewhere in the brain are no longer well regulated and do not behave in a normal manner. This results in a loss of control of movements, leading to tremor, rigidity and slowness of movements.

The hallmark of the disease, biochemically, is loss of striatal dopamine resulting from loss of nigrostriatal neurons.

Basal Ganglia = Lentiform Nucleus + Caudate Nucleus + Subthalamic Nucleus

PATHOPHYSIOLOGY OF PD



RISK FACTORS AND PROTECTIVE FACTORS

The single biggest risk factor for PD is advancing age Men have a slightly higher risk compared to women Family history is also an important risk factor

Individuals with an affected first-degree relative (parent or sibling) are estimated to have an approximately doubled risk for developing PD

This increased risk is likely to be a combination of environmental and genetic factors that close relations have in common

The single factor that has been most consistently associated with a reduced risk of PD is cigarette smoking

Caffeine consumption is also associated with highier incidence of PD

Environmental Causes of PD

Environmental causes are presumed to be one or more widely present weak toxins. The effects of these toxins may build up over time and eventually lead to disease in genetically predisposed individuals

Genetics

There are several genes that are known to cause PD, but they account for a very small minority of cases. The most important is a gene called parkin. The parkin gene creates a protein, also called parkin, that helps to break down defective proteins inside brain cells (neurons). When the parkin gene is altered, or mutated, this function is impaired. It is hypothesized that the accumulation of defective proteins contributes to death of neurons.

Other known genes for PD include alpha-synuclein, DJ-1, PINK-1, and UCHL-1

Drug Induced PD

Several drugs can block dopamine functions in the brain. Medications supposedly responsible for producing PD :

Acetophenazine	Loxapine
Promazine	Metaclopramide
Promethazine	Piperacetazine
Chlorpromazine	Thioridazine
Prochlorperazine	Mesoridazine
Triethylperazine	Thiothixene
Fluphenazine	Trifluoperazine
Perphenazine	Triflupromazine
Haloperidol	Trimeprazine

DIAGNOSIS

There is no specific test or marker for PD! Diagnosis is clinical and depends on the presence of at least two of the three cardinal signs: tremors at rest, cogwheel rigidity (as opposed to clasp knife spasticity) and bradykinesia. Glabellar Tap sign is elicitable. The examination involves recording a careful medical history, including exposure to medications that can block dopamine function in the brain. They look dementated but the intellect is absolutely intact

DIFFERENTIAL DIAGNOSES

Wilson's Disease or Hepatolenticular degeneration, due to error in copper metabolism resulting in excess copper deposition in Basal ganglia and Liver. Clinically the patient presents with parkinsonism, but the diagnosis is clinched by detecting a Golden ring at sclerocorneal junction (KF ring) seen best on slit lamp microscopy, and blood investigations showing excess copper levels Essential tremors, in which tremor is the only symptom Progressive supranuclear palsy, characterized by inability to look downward Multiple system atrophy, characterized by early and prominent autonomic symptoms Vascular (related to blood vessels) parkinsonism, caused by multiple small strokes Poisoning by carbon monoxide, manganese, or certain pesticides

CLINICAL CLASSIFICATION OF MOVEMENT DISORDERS

1. **Akinetic or Rigid Form**

   Parkinsonism PD, Parkinson's Syndrome

   Stiffman Syndrome

   Characterized by slowly, progressive muscle stiffness associated with superimposed spasms. Usually begins in low back and ascend along spine and affects even limbs. Jaw is especially spared.

2. **Hyperkinetic Form**

   Chorea Syndromes

   Rapid, irregular, jerky movements that cannot be voluntarily suppressed affecting distal extremities or face.

   Dystonia

   Continuous deviation of posture about one or more joints. It occurs as a result of repetitive, patterned or sustained contraction of various muscles.

   Myoclonus

   Sudden, brief, shock-like jerks caused by muscular contractions or due to inhibition of ongoing muscular activity

   Ballism / Hemiballism

   Sudden, often, violent, flinging movement of a proximal limb.

   Tics

   Abnormal, involuntary movements affecting single focal location which can be voluntarily controlled.

TREATMENT

Unlike in many other neurodegenerative diseases, effective treatment for the symptoms of Parkinson's disease is available. Unfortunately, no therapy has yet been conclusively shown to slow or reverse the disease.

Goal of Therapy: To replace the brain's depleted supply of dopamine with the drug levodopa, which the brain uses to make more dopamine. Alternatively, dopamine-like drugs (agonists) can mimic dopamine's effects on its target cells (in the caudate and the putamen)

Several important factors influence decision-making

Levodopa (LD) continues to be the most effective treatment for motor symptoms, and all patients eventually require it. Long-term complications of levodopa therapy are a concern, and may influence whether therapy begins with levodopa or a dopamine agonist. Non-motor symptoms, especially depression, are increasingly being seen as important targets of therapy. Surgical treatment has become a mainstay of late-stage management, although not all patients are appropriate candidates. Fetal Nerve / Stem cell transplant therapies are still experimental. Non-pharmacological treatments remain an important part of the whole treatment program.

Long-term Complications of Treatment

Motor fluctuations "Wearing off"- instead of a smooth, predictable symptomatic benefit, the patient may lose benefit earlier than usual Sudden switch from 'on' to 'off'- sudden onset of symptoms in a wellcontrolled patient Dyskinesias are wild, uncontrolled, involuntary movements that occur when dopamine levels are too high.

MEDICALTREATMENT

Dopaminergic Agents

Levodopa (LD)

Dopamine Agonists LD is converted in the brain into dopamine It was introduced as a PD therapy in the 1960s, and remains the most effective therapy. It lessens and helps to control all the major motor symptoms of PD, including bradykinesia, which is generally the most disabling feature of the disease. Carbidopa (CD) is included in the standard oral formulation to increase the effectiveness of a dose of LD hence reducing its dosage.

Adverse effects

Nausea and vomiting are the most common side effects. Orthostatic hypotension (low blood pressure upon standing) also occurs. The risk of hallucinations, paranoia, compulsive behavior, including gambling and hypersexuality. Drowsiness is a common adverse effect of LD. Dyskinesias are uncontrolled movements, including writhing, twitching, and shaking, occur as a result of over doses of LD. Immediate-release LD/CD is formulated in doses of 10/100, 25/100, and 25/250 mg. pills.

Dopamine Agonists

These are drugs that imitate the action of LD in the brain by directly stimulating dopamine receptors. Though they are not quite as effective as LD, they provide excellent relief of symptoms and delay the onset of motor complications.

Various Dopamine Agonists :

1 Bromocriptine
2 Pergolide
3 Pramipexole
4 Ropinirole

Adverse Effects

Drowsiness is a common adverse effect of dopamine agonists Other significant adverse effects of dopamine agonists include nausea and vomiting, orthostatic hypotension, edema, and psychosis.

Catechol O-MethylTransferase (COMT) Inhibitors

MonoAmine Oxidase inhibitor B (MAO-B) Inhibitors Anticholinergics Amantadine COMT inhibitors prolong the effectiveness of a dose of LD by preventing its breakdown. Two agents are approved, and . Both have been shown to decrease the duration of "off" time (the period of time when PD symptoms are present). Tolcapone is more effective than entacapone. Usage of these usually allow reduction of LD dose. Entacapone is dosed at 200 mg with each LD dose. Tolcapone is dosed at 100 or 200 mg, three times per day. Side effects include diarrhea for both and severe liver disease (acute fulminant hepatic necrosis), for Tolcapone.

A combination of levodopa, carbidopa, and entacapone in a single tablet (Entacom plus) is also available.

MonoAmine Oxidase inhibitor B (MAO-B) Inhibitors

MAO-B inhibitors slow the breakdown of dopamine in the brain

Rasagiline

Rasagiline is approved for the treatment of signs and symptoms of Parkinson's disease as initial monotherapy and as an adjunct therapy to LD.

Selegiline

Selegiline is approved as an adjunct in the management of parkinsonian patients being treated with LD/CD, who exhibit deterioration in the quality of their response to this therapy.

Side effects are Insomnia, hallucinations, and orthostatic hypotension

Anticholinergics

They have a limited role in PD, and are primarily effective against tremor and rigidity. Typical doses are:

1. Trihexyphenidyl: 2 to 15 mg/day (Pacitane)
2. Benztropine: 1.0 to 4.5 mg/day
3. Ethopropazine: 10 to 200 mg/day

Common side effects are memory loss, dry mouth, urinary retention, constipation, sedation, delirium, and hallucinations.

Amantadine

Amantadine has a significant effect on the reduction of dyskinesias. The usual dose is 100 mg 2 to 4 times each day. Side effects include dry mouth, hallucinations, insomnia, agitation, and difficulty concentrating

TREATMENT DECISION-MAKING AT VARIOUS STAGES OF PD

Therapy wise PD has three stages :

Stage I (Early PD) :

Disease could be managed with medical treatment only; however 20% of the patients who do not respond may require additional therapy.

Stage II (Moderate PD) :

When the medical treatment starts losing its efficacy, and is associated with dyskinesia; Most of these patients are favorable candidates for surgical intervention.

Stage III (Advanced PD) :

Patients are virtually bed bound and barely respond to medical treatment or may have significant side effects.

Some patients may still benefit by surgery.

Surgical Treatment

Brain surgery is an option for advanced PD patients whose symptoms can no longer be adequately managed with medications.

Who are the Favorable Candidates?

Those who respond well to dopaminergic therapy but in whom motor complications (off periods and dyskinesias) are limiting factors for continuation of medications.

Unfavorable patients

Impaired cognition, including forgetfulness, diminished decision-making ?ability, and language difficulties Significant brain atrophy

However advanced age by itself is not necessarily a barrier

Types of Surgeries

1) Lesioning

2) Deep brain stimulation

3) Other surgery-based procedures (still 'experimental') i) Stem cell transplants ii) Gene therapy iii) Neurotrophic factor delivery

Lesion procedures:

(i.e., pallidotomy, thalamotomy) deliver radio-frequency energy to heat and ablate the region within the target, where there is abnormal activity related to the movement problems. There are three target locations in PD surgery: thalamus, globus pallidum internus (GPi), and subthalamic nucleus (STN).

Stereotactic Surgery

This procedure is done in awake condition under local anesthesia This is possible because the brain itself is pain insensitive and patients must be able to respond to the surgical team's questions about what they are experiencing during the surgical procedure. Aframe applied to the head helps locating target in three dimensions. Target localisation is done independently using CTand MRI Scan Physiological confirmation of the defined target is achieved by intra operative Micro Electrode Recording (MER) 2 to 3 trajectories with satisfactory recordings should be identified Best of these with least side effects is selected for permanent electrode implantation.

Pallidotomy

Until the late Nineties, pallidotomy was the most common type of PD surgery. Pallidotomy involves destruction of internal part of the globus pallidus (GPi). It is performed by insertion of a wire probe into the GPi. The heat generated destroys the tissue around the probe. Effects of the surgery are almost immediate.

Improvements

Reduction in dyskinesias and dystonia Moderate control of tremor, rigidity, bradykinesia, and gait disturbance. Reduced dose requirement of LD Pallidotomy may be unilateral (one-sided) or bilateral (two-sided). Bilateral surgery is possible and improves dyskinesias further, but worsens effects on cognition, swallowing and speech, hence, done very rarely

Adverse effects

hemorrhage, weakness, visual deficits, speech deficits, and confusion. Weight gain is very common following surgery

Thalamotomy

Thalamotomy is primarily effective for tremors, and is therefore used mainly in patients for whom tremor is the only disabling symptom. During a thalamotomy, a selected portion of the thalamus is surgically ablated. Bilateral (both sides of the brain) procedures are poorly tolerated because of increased complication risks, including vision and speech problems. The procedure is gradually being replaced by subthalamic Deep Brain Stimulation (DBS)

DEEP BRAIN STIMULATION (DBS)

Uses implanted electrodes to stimulate one or more of these same regions. The electrical stimulation interferes with the abnormal activity, creating the same effect as a lesion. The effect lasts as long as the stimulation continues, but ceases when it is shut of

DBS system

A DBS system includes three components, which are implanted completely inside the body

Neurostimulator :

A pacemaker-like device that is the power source for the system. It contains a small battery and computer chip programmed to send electrical pulses to control Parkinson's disease symptoms.

Lead

An insulated wire with four electrodes, penetrating the brain

Extension

An insulated wire placed under the scalp that connects the lead to the neurostimulator (runs behind the ear, down the neck, and into the chest below the collar-bone)

There are three target nuclei group used for modulating PD. Thalamus : Ventrointermedius nucleus (Vim) Globus pallidus internus (Gpi) Subthalamic nucleus (STN)

Thalamic DBS

Like thalamotomy, thalamic DBS is primarily effective against tremor. Bilateral procedures are possible, but with a higher risk of adverse effects. Compared to thalamotomy, thalamic DBS has a lower risk of severe side effects

GPi DBS

Effects of GPi DBS tend to mimic those of pallidotomy. Dyskinesia improvement is a major effect, along with some improvement in tremor, rigidity, and bradykinesia,

primarily in the off-medication state. Bilateral DBS is better tolerated than bilateral pallidotomy.

SUBTHALAMIC DEEP BRAIN STIMULATION (DBS)

The subthalamic nucleus has become a major target for deep brain stimulation (DBS), with many teams considering it the target of choice for control of PD. It leads to improvement of all major motor features of PD, with improvement of motor scores of 40% to 60% in the off condition, and 10% in the on condition. Levodopa dosage reduction is typically around 30%, with resulting improvement in dyskinesias. Bilateral procedures appear to be superior to unilateral, with only a slightly increased risk of complications.

Benefits of DBS :

DBS can provide hours of relief from the debilitating slowness, stiffness and/or shaking of Parkinson's disease every day. Reduced dose requirement of LD It can also reduce the duration of the abnormal, involuntary movements (dyskinesias) that are a common side effect of Parkinson's medications. Better motor function and quality of life (QOL)

Side effects of DBS :

- Tingling sensation (paraesthesia) ?
- Worsening of symptoms ?
- Speech problems (dysarthria, dysphasia) ?
- Dizziness or lightheadedness (disequilibrium) ?
- Facial and limb muscle weakness (paralysis or paresis) ?
- Abnormal, involuntary muscle contractions (dystonia, dyskinesia) ?
- Movement problems or reduced coordination ?
- Jolting or shocking sensation Numbness (hypoaesthesia)

"EVOLVING" THERAPIES

Cell Transplant Therapy

Transplant of fetal substantia nigra cells has been performed in several hundred patients to date in multiple centers throughout the world. While results have been encouraging, consistent benefit was only seen in young PD patients (age 60 or below), and side effects in some patients were significant. In particular, some patients developed off-medication dyskinesias (uncontrolled movements) even without any levodopa or other dopaminergic medication.

Gene Therapy

As of 2004, gene therapy had been tried in only a few PD patients, and is still highly experimental. Delivery of the gene for glutamic acid decarboxylase (GAD) to the

subthalamic nucleus (STN). GAD is a key enzyme in the production of the inhibitory neurotransmitter 'Gamma Amino Butyric acid (GABA)'. Gene therapy with GAD is meant to increase GABA production, reducing STN activity in the manner of STN DBS. Monitoring is still in progress.

Growth Factor Delivery

Glial cell-derived neurotrophic factor (GDNF) stimulates sprouting of dopamine neurons in animal models. Direct delivery of GDNF to the brain has produced promising results in an open-label trial in a small number of patients, but by mid-2004 a larger, double-blind trial failed to show efficacy. Further research is needed, especially that concerning improved delivery of growth factors to the correct targets in the brain.

Role of Stem cells

Similar to fetal substantia nigral cells, stem cells have promising role to play in the treatment of PD. The source of stem cells are fetal umbilical cord blood and adult bone marrow. However therapy has yet to evolve.

NONPHARMACOLOGIC TREATMENTS

A wide variety of problems in PD may respond to nonpharmacological treatments. ? These include:

- Motor balance, posture, gait, and mobility ?
- Difficulties with activities of daily living ?
- Speech and swallowing ?
- Inadequate nutrition ?
- Sleep disturbance ?Pain ?
- Constipation ?
- Sexual dysfunction Depression

Physical therapy

Is as important as drug therapy and should not be under estimated or neglected. Goals of physical therapy include maintaining or increasing activity levels, decreasing rigidity and bradykinesia, optimizing gait, and improving balance and motor coordination.

Occupational therapy

Goals of occupational therapy include maximizing fine motor coordination, especially of the upper extremities, reducing energy expenditure, increasing safety and independence, and improved efficiency of activities of daily living.

Sexual Dysfunction

Affects a large proportion of patients with PD and their spouses. Difficulties include erectile dysfunction in males, vaginal dryness, and loss of libido. Hypersexuality from levodopa and dopamine agonists also occurs. Sildenafil (Viagra) has been shown to be safe and effective in men with PD to treat erectile dysfunction.

Speech and Swallowing

Several PD-specific voice training programs have been developed, which share an emphasis on consciously increasing voice volume as a key strategy. Other features are use of shorter sentences, breathing exercises, and range-of-motion exercises for the muscles of speech. Instruction to take smaller bites, to completely empty the mouth before taking the next bite, and eating softer foods improve swallowing

Drooling (Sialorrhea)

The origin of the problem is not in increased saliva production, but reduced spontaneity of swallowing. Awareness of the problem, and consciously swallowing more often, may be effective.

Driving

PD patients tend to do worse than controls on tests of driving safety, because of increased reaction times and movement times caused by PD. Patients tend not to be good judges of their loss of driving safety, and family members may need to intervene.

CONCLUSIONS

- PD is much more common then thought to be
- As life expectancy in India is improving, more and more patients have ?been diagnosed as parkinson's
- Many of PD patients respond to medical treatment and physiotherapy ?satisfactorily ?
- Few of them shall require some form of therapy sooner or later
- DBS (STN) is safest and time tested procedure for patients who are unresponsive to medical treatment

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