**Parkinson’s Disease**

(By Dr. S. UMA DEVI)

**Definition:** Parkinson’s disease is a syndrome of Progressive, neuro-degenerative, movement disorder consists of:

1. Tremors
2. Poverty of movement
3. Rigidity and
4. Postural instability (imbalance, loss of rightening reflex)
5. At least 2 out of 4 prime signs are diagnostic; Cardinal signs can occur in conditions other than Parkinsonism.

Primary Parkinsonism is called Parkinson’s disease

**Synonyms:** Paralysis agitans, Idiopathic Parkinsonism.

**Prevalence:** Age incidence: 50-85yrs; prevalence increases at age >50yrs

**Gender:** slight male predominance

**Parkinsonism:**

Any of a group of nervous disorders similar to Parkinson’s disease, consisting of tremors, rigidity and poverty of movements and often having a specific cause like use of certain drugs/exposure to toxins is called Parkinsonism.

**Clinical picture of Parkinson’s disease:**

Mean age of onset- is about 55 yrs.

Juvenile Parkinsonism is also known.

**I. Tremors:**

- Initially: unilateral/later bilateral
- Initially fine/later coarse.
- Initially: hands/later feet, (tongue, lips, eyelid/chin still later)
- Very often: rest tremors/rarely action tremors.

**Types:** pill rolling or drum beating

- Pill rolling: flexion, extension of fingers with -rotary component between thumb and fingers seen
- Drum beating: Flexion extension of the wrist with -Supination, pronation of forearm.

**Aggravating** factors: Emotion, Excitement.

**Alleviating** factors: Sleep/action.

Asymmetry relates to: hand dominance, initial disease, younger age, asymmetric degeneration in basal ganglion
II. Poverty of movements

❉ Bradykinesia/Akinesia

❉ Initially associated movements - affected.
(Swinging movements of the arm while walking.)

❉ Later voluntary movements - Both initiation and execution affected.

As result the following signs:
- Mask like facies
- Fixed stare.
- Infrequent blinking
- Impaired ocular convergence.
- Reduced swinging movements of the arm.
- Micrographia
- Monotonous speech

(at times total anarthria)

Note: Hypokinesia can be dominant sign in some patients.
So patient may be house bound or wheel chair bound.

Kinesia Paradoxica:
This is a paradoxical phenomenon.
Though there is slowness of movements, Patient can run and catch
a moving bus or catch a fast-bowled ball.
But this is only a temporary phenomenon provoked by emotional
stress.

Akathesia
Intolerable restlessness plus continuous change of posture. (A rare
clinical feature)

III. Rigidity:

❉ Two types.
  a. Plastic type
  b. Cog wheel type

❉ Plastic type: Tone is uniformly increased throughout the range
of movement.

❉ Cogwheel: tone is interrupted.

❉ Which group of muscles involved?
Both agonists and antagonist equally affected.

❉ How to enhance rigidity for clinical demonstration?
- By active movements of opposite limb.
Rigidity like tremors can be asymmetrical.
Rigidity contributes to two things-
  a.) Flexed attitude
  b.) Festinant gait.

Attitude of universal flexion
I.e. Head flexed upon the neck, Neck flexed upon the trunk
Trunk flexed, Hip, Knee and ankles flexed, Shoulders adducted.
Elbows and wrists flexed and Meta carpo phalangeal joints flexed.

IV. Postural disorders:
* Difficulty in standing without support
* Tends to fall often
* Difficulty in initiating walking (freezing)
* Difficulty in getting up from chair.
(Show poor response to treatment)

❖ No sensory symptoms occur in Parkinsonism.

Gaits in Parkinsonism:
Two Types
I. Short shuffling gait:
Slow, short steps with loss of associated movements of the arms
II. Festinant Gait: Hurrying gait.
Spontaneous propulsion during walking.
This is because of increased tone and lack of reflex adjustment involved in effective walking; hence quick gait with increasing pace as if patient is trying to catch up his own centre of gravity

Certain phenomena occurring while walking:
(As a result of defective rightening reflex)
Propulsion: When pushed from behind, the pace of walking goes on increasing until the patient is halted by a wall or some obstacle.
Retropulsion: When pushed from front goes on moving backwards faster and faster until halted.

Freezing:
Patient’s feet freeze to the ground and there is difficulty in initiating walking.

Initial presentation:
70% tremors; 20% stiffness, slowness, 13% micrograhia /loss of dexterity, 12% gait disturbance, 8% muscle pain, cramps, 1.5% others – depression, drooling, dysphagia, dysarthria, disturbance in psyche.

Diagnostic signs of Parkinson’s disease
❖ Distal tremors
❖ Mask like facies
❖ Fixed reptilian stare with infrequent blinking.
❖ Stooped posture
❖ Positive Glabellar reflex.
❖ In addition Dysarthria, cogwheel rigidity and shuffling gait,
-if present confirms the diagnosis.
Diagnostic in **early** stages: Asymmetry, resting tremors and response to dopaminergic drugs.

The diagnosis of Parkinsonism is essentially a clinical one. No confirmatory imaging test or laboratory test is available.

**PARKINSONISM**

Any of a group of nervous disorders similar to Parkinson’s disease consisting of tremors, rigidity and poverty of movements and often having a specific cause like use of certain drugs/ exposure to toxins is called Parkinsonism. As mentioned above idiopathic or primary Parkinsonism is called Parkinson’s disease.

**Etiology of Parkinsonism.**

I. **Idiopathic** (Paralysis agitans / Parkinson’s disease)

II. Atherosclerotic.

III. Post encephalitic

IV. Traumatic-Punch drunk syndrome in boxers.

V. Neoplastic. Tumors of Brainstem (very rare)

VI. Toxic;

   MPTP (methyl phenyl tetra hydro pyridine) in drug abusers-occurring as a contaminant in street drug.

Other toxins; carbon monoxide, heavy metals-manganese, insecticide -paraquat

VII. Drug induced;

VIII. Phenothiazines, reserpine, Butrophenones.

IX. Infections: -

   Syphilitic mesencephalitis
   Viral-Japanese B encephalitis,
   Encephalitis Lethargica- Sleeping Sickness.
   Tuberculosis (rare)

X. Wilson’s disease

XI. Genetic susceptibility.

**Other uncommon signs of Parkinsonism.**

a. Mental disturbance.

b. Ocular signs.

c. Skeletal deformities.

d. Alimentary disorder.

e. Postural disorders.

f. Weight loss.

g. Speech disturbance
   
   ✴️ Hypophonia
   
   ✴️ Palilalia-Involuntary repetition of phrase with increased rapidity.

**Ocular signs of Parkinsonism**

• Wide palpebral fissure
- Infrequent blinking
- Tremors of eyelids
- Blepharo spasm. (Post encephalitic)
- Oculogyric crisis-Eyes turned upwards and outwards.
  (Post encephalitic parkinsonism)
- K.F. Ring, Wilson’s Disease
- Pupillary changes:
  - Reversed Argyl Robertson’s pupil
  - Impaired light reflex.
- Positive glabellar reflex.
- Hypometric saccades
- Impaired smooth pursuit.

**Mental disturbances**
Dementia –Uncommon in Parkinson’s Disease
If present –is a late feature.
Affects 1/3 rd cases.
More common in MSA, PSP

**Skeletal deformity:**
Due to contractures secondary to rigidity.
- Hand Swan neck deformity.
- Fingers digging into the palms
- Feet –talepes equino varus.
- Foot rests upon medial border.
- Occurs in post encephalitic.

**Alimentary disorder:**
- Excessive salivation.
- Dysphagia.
- Aspiration-pneumonia, on account of pooling of saliva in pyriform fossa
- Heartburn
- Reflux esophagitis
- Hiatus hernia
- Constipation- can cause mega colon-may be mistaken for bowel obstruction
- Weight Loss:
  Very common in parkinsonism, so think before investigating for occult malignancy.

**Reflexes:**
Glabellar positive.
Deep tendon Reflexes normal.
Plantar flexor.
Plantar extensor in – atherosclerotic, post encephalitic Parkinsonism.

**Autonomic disturbances:**
Increased Seborrhea, sialorrhea
Postural hypotension (MSA) (Multiple system Atrophy)
Hypertension, Flushing, Tachycardia,
Hypothermia
Retention of urine.

**Sensory disorder**

Pain
Paresthesia
Impaired olfaction

**Differential diagnosis for Mask like facies:**

Parkinsonism
Bilateral facial palsy
Scleroderma
Hypothyroidism
Dementia
Depression
Facial myopathy

**Note:** Idiopathic parkinsonism does not manifest with hemiparesis, spasticity or autonomic disturbances

**Features to look for under general examination:**

BP: to exclude atherosclerotic Parkinsonism
Jaundice – indicates Wilson’s disease
K.F. ring – indicates Wilson’s disease
Mask like facies
Seborrhea, sialorrhea – indicates post encephalitic parkinsonism

**Post encephalitic Parkinsonism:** Just after world war I, a pandemic of viral encephalitis occurred which resulted in the development of post encephalitic parkinsonism in the survivors. This entity is rarely seen nowadays.

**Pathology and pathogenesis of Parkinsonism:**

Pathogenic **hallmark** of the disease is:

Loss of pigmented cells in Corpus Striatum,
Resulting in deficiency of Dopamine and excess of Acetyl choline.

**Neurotransmitter disturbances in Parkinson’s:**

- Dopamine and acetylcholine are neurotransmitters, which have antagonistic action.
- In parkinsonism their balance is lost.
- Dopamine level falls and acetylcholine increases.
- Neurodegeneration occurs in cells of Substantia nigra
- Substantia nigra connects to corpus striatum, where Dopamine is released. Dopamine suppresses unintended movements.
- After loss of 80-90% cells – symptoms start
- Cell degeneration of substantia Nigra and fall in dopamine concentration is the hallmark in this disease.
Macroscopic, Microscopic pathology;
Loss of pigmented dopaminergic neurons in substantia nigra macroscopically and
Presence of cytoplasmic eosinophilic inclusion bodies called Lewy bodies microscopically.

Oxidative hypothesis in understanding cell death in parkinsonism:
Glutathione has protective effect during dopamine metabolism.
It clears free radical H\textsubscript{2}O\textsubscript{2} formed. A fall in protective glutathione level leads to accumulation of hydroxyl radicles that react with cell membrane lipids causing lipid peroxidation which causes cell damage.
In addition increased iron -pro oxidation molecules occurs in PD.

Complications of Parkinson’s:
1. Depression, Dementia
2. Drug induced complications
3. Dysphagia, difficulty in chewing
4. Constipation
5. Difficulty in urination - (retension, incontinence)
6. Sexual dysfunction

Stages of Parkinson’s disease:
Stage I: Unilateral involvement.
Stage II: Bilateral involvement.
Stage III: Bilateral with mild postural changes.
Stage IV: Bilateral and postural changes; unable to live alone; needs help.
Stage V: Severe full blown disease.
For stage I and II: No drugs or only anticholinergics or Amantadine or both.
For III, IV and V: L-Dopa required
This staging system is replaced by Unified Parkinsons Disease rating scale (UPDRS) which is much more complicated.

**INVESTIGATIONS**
I. CT/MRI to r/o or r/in structural lesions
II. Perform FP-CIT SPECT
(Fluro propyl carbo methoxy iodophenyl tropane single photo emission CT)
If dopamine deficiency is doubted as a cause of tremor
III. Genetic testing if and when indicated

**Treatment options for Parkinsonism.**
I. Treatment of identifiable causes if any.
II. Medical
III. Surgical
IV. Other modalities.

I. Treatment of identifiable causes;
A. Drug induced: - Withdraw the drug, but cure occurs after many months only.
B. Carbon monoxide, Manganese poisoning.
C. Structural lesions like infarct, tumor.
D. AV malformations – Abrupt onset.
E. In drug addicts, a chemical contaminant of heroin- MPTP (methyl phenyl tetrahydropyridine)

**Medical:**

**Modalities**
Enhance dopaminergic Action by;
A. Increasing dopamine synthesis-L-Dopa
B. Increase dopamine release- (Amantadine.
C. Reducing Dopamine break down by – Selegeline.
D. Direct stimulation of dopamine receptors by
   Apomorphine
   Pramipexole
   Rapinirole
   Bromocryptine.(Withdrawn from the market)
   Pergolide.( Withdrawn from market )

**Drug therapy in Parkinsonism.**
**Principles:**
1. Avoid anticholinergics in old age.
2. Selegeline can be used at all ages.
Avoid early use of L-Dopa.
Avoid B6 and high protein diet.
Drug therapy depend on-stage of the disease

**Disease manifestations and drugs:**
For tremors- anticholinergics.
For akinesia and postural imbalance- L-Dopa
For rigidity- L-Dopa is not very effective.

**Stage of the disease and drugs:**
For **initial** stages –stage I and II:
   - No drug or
   - Only anticholinergics or
   - Amantadine or
   - Selegeline.
For **later** stages (III, IV, V):
   - L.Dopa required
   - with Anticholinergics.
   - Selegeline.

**LEVO DOPA:**
   - **Action:** Replenishes lost neuro transmitter dopamine.
   - **L.Dopa** is converted to dopamine.
   - Though number of dopamine releasing terminals are reduced, in corpus Striatum, it is possible to overdrive the available neurons to produce Dopamine.

**Metabolism of LevoDopa:**
   - 90% of oral L.dopa is decorboxylated in GI tract.
   - Only 10% reaches brain.
   - This peripheral conversion causes high incidence of nausea, vomiting and low levels of L.Dopa reaching the brain.

**L.Dopa ,Carbi dopa combination.**
   - Above problem is overcome by combining L.Dopa with a peripheral acting Decorboxylase inhibitor.
   - Carbidopa does not cross blood brain barrier.
   - This combination “Sinimet” allows much lower doses of L.Dopa to be used and reduces side effects.

**Ratio of Combination:**
   - L.Dopa :Carbidopa in 4:1ratio; 10:1 ratio also available.
   - Available strength:
   - This preparation is available in strength of 50mg, 100mg, and 250mg of L.Dopa.

**Building up of the Dose.**
Start with 50mg bid/tds
Increase slowly over 1mth to 100mg tds
Increase every 3\textsuperscript{rd} or 4\textsuperscript{th} day.
Review the patient after 2 weeks to note any side effects.
If well tolerated, can increase dose by $\frac{1}{2}$ tds
Dose is increased until significant improvement occurs or side effects appear.
The lowest dose producing satisfactory effect is continued.
Maximum dose is 800 to 1000 mg per day.
But high doses cause troublesome side effects.

**Side effects of L.Dopa:**
1. Nausea, vomiting
2. Hypotension
3. Involuntary movements
   - Orofacial dyskinesia,
   - Limb and axial dystonia.
4. Depression, hallucination, delusion.

**Late deterioration—“On –off phenomenon”**.
- After 3-5 yrs, deterioration in response occurs.
- This in 1/3 to $\frac{1}{2}$ the patients.
- Elicitable in effect at different points of time of the day.
- This is called on-off phenomenon.
- This is due to progress of the disease and inability to store Dopamine.
- Akinesia alternates with agitation and Dyskinesia.
- This results from denervation hypersensitivity in remaining dopamine receptors.

**Management of on-off phenomenon:**
\begin{enumerate}
  \item Reduce the dose of L.Dopa.
  \item Shorten interval between doses.
  \item Restrict high protein diet which can slow the transport of L.Dopa across G.I. mucosa and blood brain barrier.
\end{enumerate}

**Efficacy of L-Dopa:**
- Loss of efficiency occurs with time.
- So the single dose that was effective for say 2hrs, needs to given more frequently.

**ANTI CHOLINERGICS.**

**Action:**
Block muscarinic receptors and so reduce cholinergic transmission.
Effective in relieving tremors.

**Indication:** As synergist with L.Dopa.

**Common Drugs:**
\begin{enumerate}
  \item Pacitane.(Trihexy phenedyl)-1 to 2mg Qid.
  \item Benztropine.-0.5 to 1mg tds.3. Orphinadrine 50-100mg tds.
\end{enumerate}

**Contra indications:** Elderly patients- because of urinary retention.
**Side effects:** Dry mouth, blurring of vision, glaucoma, confusion and dementia.
(Avoid in elderly)

**ANTI HISTAMINICS:**
Some antihistaminic also have anticholinergic properties.
They are useable as alternatives
Their sedative effect is advantageous in patients with insomnia.
Common drugs;
1. Diphenhydramine (Benadryl) 2. Phenindiamine.

**Anti depressant:**
Amitriptylin – has anticholinergic action; usable in elderly patients

**MAO INHIBITORS: Selegeline**
1. Retard nigral cell loss.
2. MAO metabolises dopamine.
3. MAO inhibitors act by inhibiting metabolism of dopamine.
4. They are of 2 types.
5. MAO type B metabolises Dopamine. (Selegeline is MAO type b inhibitor)
6. MAO type A has selective specificity for Nor adrenaline and Serotonin.
7. MAO B inhibitors decrease oxidation of Dopamine.
   By doing this they reduce likelihood of nigral damage caused by toxic, free radicals.
8. Selegeline can delay the need for Sinimet for about a year; can be used in combination; but does not retard disease progress.

**COMT Inhibitors:**
Catacholamine O- methyl transferase inhibitor
Inhibit the enzyme COMT, which breaks down dopamine.
Tolcapone: Potent (but can cause Liver damage/liver failure; not recommended)
Entacapone; No live problems

**AMANTADINE:**
Anti viral agent.
Releases stored Dopamine from presynaptic terminals.
Increases synthesis and reuptake.
Effective in early and mild stages of the disease only.
Effective for tremors.
Side effects: Livido reticularis skin, Ankle edema.

**Co enzyme Q10:**
Present in mito chondria of cells
Levels low in Parkinsonism
So in early, mild cases supplementation helps.
**SURGICAL TREATMENT OF PARKINSONISM:**

With advent of L-dopa in 1960 surgical treatment was slowly given up. Now there is a renaissance since L-dopa is becoming a failure.

**Indication:**
When symptoms cannot be controlled with medications.

**Three modalities of surgical therapy:**
1. Ablative
2. Deep brain stimulation
3. Restorative surgery
   - A. Intra striatal graft of dopamine producing cells:
     - Foetal cell implant in basal ganglion.
   - B. Intracerebral delivery of growth factor

1st and 2nd try to compensate for cellular and biochemical abnormality.
3rd Attempts to replace or promote the survival of degenerating cells.

**Ablative technique**

**Pallidotomy:**
A small amount of tissue in Globus pallidum is destroyed with electric current; (Neural pathways between G.pallidum and thalamus interrupted.)

**Thalamotomy:** a small amount of tissue in thalamus is destroyed

**Sub thalamotomy:** more recent procedure

Ablative surgery has many side effects and so not popular

**As an alternative emerged DBS**

**Deep brain stimulation.**
A brain implant device is used.
Tiny electrodes are implanted deep within the brain-subthalamic nucleus. that controls many aspects of motor functions.

Electrical impulses are transmitted through a wire from a pace maker like device implanted in the chestwall.

<table>
<thead>
<tr>
<th>Surgery does not cure the disease.</th>
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<tbody>
<tr>
<td>Can cause undesirable sequelae</td>
</tr>
</tbody>
</table>

**Biological neuro restorative techniques**
Auto adrenal transplant: attempted with variable results
Gene therapy
Growth factors

**Other modes of treatment:**
1. Physio therapy.
2. Speech therapy.
3. Psychotherapy.

1. To reduce the rigidity and correct postural abnormalities.
2. Speech therapy if dysarthria and dysphonia is present.
3. Psychotherapy

**Differential Diagnosis of types of Parkinsonism.**

<table>
<thead>
<tr>
<th>Features</th>
<th>Idiopathic</th>
<th>Atherosclerosis</th>
<th>Post encephalitic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>50-60 yrs</td>
<td>50-60 yrs &amp; above</td>
<td>Younger age group.</td>
</tr>
<tr>
<td>Structure/tract affected</td>
<td>Mainly extra</td>
<td>Also Pyramidal</td>
<td>Also pyramidal &amp; other structures in CNS.</td>
</tr>
<tr>
<td>plantar</td>
<td>Flexor</td>
<td>Can be extensor</td>
<td>Can be extensor</td>
</tr>
<tr>
<td>Associated features</td>
<td>-</td>
<td>Signs of Atherosclerosis</td>
<td>Sialorrhea Seborrhea Oculogyric crisis</td>
</tr>
</tbody>
</table>
**Parkinsonism plus syndrome.**

These are disorders in which classical signs of Parkinsonism are combined with other neurological dysfunctions.
Other structures that can be involved are
1. Autonomic
2. Cerebellar
3. Cortical
4. Oculomotor.
Parkinsonism appearing in patients with other neurological disorders

**Parkinsonism plus syndromes:**
- Progressive supranuclear palsy
- Multi system atrophy
- Shy dragger syndrome
- Olivo ponto cerebellar atrophy
- striato nigral degeneration.
- Cortico basal ganglion degeneration
- ALS/PD/Dementia complex of Guam
- Alzheimer’s/Pick’s Disease.
- Creutzfeldt- Jakob disease
- AIDS

**Diagnosis:**
Suspect parkinsonism plus if there is
1. prominent dyskinesia and rigidity without tremors at the onset.
2. Rapid progression.
3. Neurological signs apart from that of the basal ganglion.

### Multi system atrophies

<table>
<thead>
<tr>
<th>Common Name</th>
<th>Early clinical features</th>
<th>Late clinical features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shy-Drager Syndrome</td>
<td>Dysautonemia</td>
<td>Parkinsonism,cerebellar signs,MND with amyotrophy &amp;cortico Spinal signs Ocular palsies dementia</td>
</tr>
<tr>
<td>Olivoponto cerebellar Atrophy</td>
<td>Cerebellar dysfunction plus Parkinsonism.</td>
<td>Dys autonomy pluscortico spinal signs.</td>
</tr>
<tr>
<td>Striato nigral degeneration.</td>
<td>Parkinsonism</td>
<td>Dys autonomia, Cerebellar signs</td>
</tr>
</tbody>
</table>

**JUVENILE PARKINSONISM**
Parkinson’s Affecting persons under the age of 20 yrs.
Often familial; can be primary
Autosomal dominant or recessive
Results from mutation of gene PARK 2; Responds to L-Dopa