Parkinson`s Disease : Recent Advances
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Abstract
Parkinson`s disease is most common degenerative disorder. Diagnosis is clinical in majority of the patients. Small number of patients have family history and several types of familial Parkinson`s disease is now known. Most of the patients have onset of symptoms in sixth decade. Response to dopa agonists and L-dopa is good and there are different reasons to choose any of the drug as first line treatment. Motor fluctuation presenting as wearing off and dyskinesias are main challenges in long term management.

Introduction
Parkinson`s disease (PD) is characterised by tremor, rigidity, bradykinesia / akinesia and loss of postural reflexes. Recently non motor symptoms of PD have been identified and some times they may be the only symptom at onset. Basic pathology of PD relates to dopaminergic pathway. Many secondary causes of PD are well known.

History: In 1817 James Parkinson first described PD as “Involuntary tremulous motion, with lessened muscular power, in parts not in action and even when supported; with a propensity to bend the trunk forwards, and to pass from a walking to a running pace: the senses and intellects being uninjured” known as shaking palsy. Major criticism of this definition has been undue focus on muscle power and no importance to other symptoms like rigidity.

Milestones in Parkinson`s Disease
1817- J Parkinson first described “An essay on the shaking palsy”
1841- Term `Paralysis agitans’ used for the first time by Marshall Hall
1888- Charcot referred the disease as “maladie de Parkinson” or Parkinson’s disease (PD)
1919 – Recognised PD having cell loss in substantia nigra
1939- Surgery at basal ganglia by Meyers
1957- Carlsson and colleagues discovered dopamine
1960- Ehringer and Hornykiewicz identified reduced dopamine in striatum
1961- Levodopa used for the first time in injectable form and a year later in oral form
1987- Deep-brain stimulation (DBS) was first developed in France.

Epidemiology
Parkinson’s disease may have an onset before 20 years (Juvenile PD), 20-45 years (Young PD) or more than 45 years (Idiopathic PD). Peak age of onset is seen in sixth decade. From India Bharucha et al reported the prevalence of PD in the Parsi community (6-328/105). Non-Parsi communities are having prevalence rates of 14-41/105. In United States there are approximately 1 million patients of PD.

Pathogenesis and Genetic Consideration
Young PD is usually inherited and idiopathic PD is usually sporadic. Inherited form of PD has given new insight into pathogenesis. Most common mutation is seen in (Table 1) µ- synuclein (PARK 1), parkin (PARK 2) and UCH-L1 (PARK 5) protein. There is evidence of involvement of mitochondrial function because of oxidative stress. Lewy bodies in neurons and degeneration of dopaminergic cells are pathological hallmarks. Some forms of PD are because of drugs (antipsychotics, SSRIs, valproic acid and antiemetic), encephalitis (Japanese encephalitis), repeated head injury and exposure to toxins (Manganese).

Clinical Features
Classical clinical features of PD are motor, however non motor symptoms and psychiatric features are also important. Rest tremor is considered to be most characteristic but action tremor may also be seen. Cogwheel rigidity and bradykinesia are other major presenting symptoms. Loss of postural reflexes is usually a late feature (Table 2). Many scales are used for assessing progression and disability in PD patients. Most commonly used

Table 1: Genetic causes of “Familial Parkinson’s disease”

<table>
<thead>
<tr>
<th>Type</th>
<th>Inheritance</th>
<th>Protein</th>
</tr>
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<tbody>
<tr>
<td>Park 1</td>
<td>AD</td>
<td>µ- synuclein</td>
</tr>
<tr>
<td>Park 2</td>
<td>AR</td>
<td>Parkin</td>
</tr>
<tr>
<td>Park 4</td>
<td>AD</td>
<td>µ- synuclein</td>
</tr>
<tr>
<td>Park 5</td>
<td>AD</td>
<td>UCH-L1</td>
</tr>
<tr>
<td>Park 6</td>
<td>AR</td>
<td>PINK1</td>
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<td>Park 8</td>
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<td>Park 9</td>
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<td>ATP13A2</td>
</tr>
<tr>
<td>Park 10</td>
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<td>?</td>
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<tr>
<td>Park 11</td>
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Table 2: Red flag signs in Parkinson’s disease

| Early dementia |
| Early fall |
| Symptoms predominantly in lower limb |
| Hallucinations at onset |
scales are Hoehn and Yahr (H&Y) scale and “Unified Parkinson Disease Rating Scale” (UPDRS). Certain posturing and focal dystonias are considered to be quite characteristic of PD. Camptochromia, Pisa syndrome and striatal toe are different types of dystonias and posturing seen in a PD patient.

Non motor symptoms are mainly anosmia, sleep disturbances, constipation, neuropsychiatric and sensory symptoms. They may predate the motor symptoms in some patients. Major neuropsychiatric symptoms are anxiety, depression and dementia. In some group of patients depression may be the presenting symptom of PD and its treatment may unmask the motor symptoms. Dementia with PD is quite common however alternative diagnosis like diffuse lewy body should be considered if it is present at onset (Table 2). Psychotic symptoms may be present independently or they may be due to treatment. Other psychiatric symptoms may include sexual disorder or gambling.

**Differential Diagnosis**

**Progressive supranuclear palsy (PSP):** Characteristic features of PSP are axial dystonia, vertical gaze paresis and lack of tremor. Early fall and focal dystonias are also common than PD patients. Neuropathological study reveals role of tau protein. Recently two different subtypes have been described one Richardson’s syndrome (RS)and PSP-parkinsonism (PSP-P). Small group of PSP-P patients respond to L-dopa preparation, however response is only temporary.

**Vascular Parkinsonism (VaP):** Also known as lower body parkinsonism and characterised mainly by gait difficulty, absence of tremor and no response to L-dopa preparations. Risk factor like hypertension and diabetes mellitus is usually present. Associated vascular dementia may also be seen.

**Diffuse lewy body disease (DLB):** DLB is characterised by dementia and parkinsonian features. Compared to PD dementia is seen here quite early. DLB patients also complain visual hallucinations and high sensitivity to antipsychotic agents.

**Multiple system atrophy (MSA):** There are three subtypes of MSA; MSA (P), MSA (A) and MSA (C). MSA (P) was previously known as striato nigral degeneration and MSA (A) was known as Shy Dragger syndrome having predominantly autonomic dysfunction. MSA(C) is having associated cerebellar features. All MSA subtypes do not respond to L-dopa preparations.

**Essential Tremor (ET):** Patients of ET present with predominantly action tremor with symmetrical onset and response to alcohol. Positive family history may be present. Treatment options include propranolol and primidone.

**Investigation**

Diagnosis of PD is usually clinical and lab investigation has no direct role, however certain investigations are helpful in early diagnosis and differentiating it from Parkinson plus syndrome.

**MRI:** Usually normal but in same cases iron accumulation in substantia nigra may be visualized as T2 W hyperintensitiy.

**PET (11C FL – fluorodopa:** Reduced uptake in putamen is highly characteristic of PD.

**SPECT** – Decreased striatal metabolism is a hall mark of PD.

**Treatment**

**Drugs**

**Dopa agonists:** Dopa agonists can be given orally, intravenous or as transdermal delivery system. Oral dopamine agonists are ergot and non ergot derivatives. Bromocriptine, pergolide, piribedil, pramipexole, ropinirole and dihydroergocryiptine are ergot preparations and carry a risk of long term side effects in form of retroperitoneal fibrosis. Pramipexol, ropinirole and piribedil are non ergot oral preparations. Apomorphine is also nonergot and used as intravenous route. Rotigotine and lisuride are given as transdermal preparations. Dopamine receptors are classified as D1, D2, D3, D4 and D5. Most of the dopa agonist act in PD through D2 and D3 receptor activity. Bromocriptine and pergolide are having more D2 activity where as ropinirole and pramipexole are having more D3 activity. Non motor side effects are more common with dopa agonists and include edema, somnolence, constipation, dizziness, nausea and hallucinations.

**L- dopa (Dopamine precursor):** Along with Decarboxylase Inhibitor, L-dopa is most important drug used in PD treatment. To prevent peripheral side effects decarboxylase inhibitor (carbidopa and benserazide) is combined with L-dopa. Nausea, vomiting and delirium are most common side effects. Tremor is least responsive symptoms. But most of the patients have significant response to the initial treatment and there is a marked relief in bradykinesia, rigidity and fatigability. However its use is limited after 5-10 years after onset of motor fluctuation.

**COMT Inhibitors:** Catechol -o-methyltransferase (COMT) metabolises L- dopa to 3-O-methyl dopa. COMT inhibitors block this enzyme and increase plasma half life of L-dopa. Tolcapone and entacapone are two COMT inhibitors. Entacapone is available in market in combination with L-dopa and carbidopa. Tolcapone use requires continuous monitoring for liver functions. Other side effects are related to increase dopaminergic effects including sleep disturbances.

**MAO-B Inhibitors:** Selegiline and rasagiline are two MAO-B inhibitors available for commercial use. Both are irreversible inhibitors. Selegiline is used as initial treatments option however its effect has been inconsistent. Rasagiline is used in a dose of 1-2 mg/day. It is used for motor fluctuation. They should not be given with tricyclic antidepressants (TCA) and selective serotonin reuptake inhibitors (SSRI).

**Anticholinergics:** Most common indication of anticholinergic drug in PD is tremor not responding to L-dopa.Usual dose is 0.5 mg- 6 mg in three divided dosages. Side effects in form of psychosis are some times serious in elderly population.

Starting Medical Treatment in PD Patients (Dopa agonists or L-dopa): There is a considerable amount of uncertainty while starting treatment for recently diagnosed patient of PD. Dopa agonists are having less motor fluctuation and have L-dopa sparing effect for initial few years of treatment. But they have some serious side effects in form of hallucinations and day time sleepiness. Their limitation is inadequate relief in motor symptoms in comparison to L-dopa. So they are considered as first line drug for young PD patients having mild symptoms and no dementia or other cognitive disorder. However they are not suitable for elderly and patients having dementia or severe motor symptoms.

**Surgery**

Surgical treatment of PD comprises 3 different approaches;
Inhibitors may be useful in sensory symptoms and fatigability. Amantidine and MAO-B inhibitors are quite effective in management of dyskinesia and administration of modafinil. Restless leg syndrome is common in PD patients and can be benefited by adjusting drug dosage or adding benzodiazepines. Patients taking dopa related problems can be managed by maintaining good sleep hygiene and adding benzodiazepines. Amantidine and MAO-B inhibitors may be useful in sensory symptoms and fatigability.

**Treatment of Non-Motor Symptoms**

Depression can be treated either by TCA or SSRIs. Sleep related problems can be managed by maintaining good sleep hygiene and adding benzodiazepines. Patients taking dopa agonist complain of daytime sleepiness and may be benefited by adjusting drug dosage or adding modafinil. Restless leg syndrome is common in PD patients and can be benefited by dopa agonists mainly ropinirole. Amantidine and MAO-B inhibitors may be useful in sensory symptoms and fatigability.

**Motor Fluctuations**

Motor fluctuations in PD patients on L-dopa treatment develop at the rate of 10% per year and 50% have this after 5 years. Broadly motor fluctuations can be of two types; wearing off and dyskinesias.

**Wearing off**

Management of wearing off symptoms requires adjusting L-dopa dosage according to patient requirement. Small amount of dosage at frequent interval or adding a COMT inhibitor to prolong serum level of drug or using controlled release preparations are some of the options available. Injection apomorphine and L-dopa liquid preparations can also be used.

**Dyskinesias**

Dyskinesias may be peak dose, off dose or biphasic. Amantidine is quite effective in management of dyskinesia and a dose of 200-400mg in two divided dosages can be given. Another option is to give small dose of L-dopa at frequent interval or combine it with dopa agonist or COMT inhibitors.

**Conclusion**

Parkinson’s disease is most common type of movement disorder seen in clinical practice. Early diagnosis can be made with high index of suspicion. Most of the patients respond to dopa agonists or L-dopa preparations. Motor fluctuation is seen after 5-7 years of treatment. Most of the symptoms can be managed by change in drug dosage or surgical approach. Stimulation of subthalamus using DBS has become an important tool for treatment. Many new modalities of treatment like adrenal autografts, porcine fetal nigral xenografts and human fetal nigral grafts are promising future treatment options.

**References**


