Introduction

Early descriptions include tremor and akinesia in ancient Indian Ayurvedic literature from 4500-1000 BC. It was called Kampavata in the ancient Indian medical text Basavarajiyam. An eclectic London surgeon and apothecary, James Parkinson (1755-1828), formally described the disease in 1817 in a classic monograph “Essay on the Shaking Pal-sy”. Parkinson’s disease (PD) is probably the most famous movement disorder presently known to man. From Muhammad Ali and Michael J. Fox to Pope John Paul II, there are numerous celebrities who have brought this disorder to light. This is the second most common neurodegenerative disorder after Alzheimer's disease. There is a significant financial and social burden of PD. It has been especially with the aging population and described as one of the most disabling chronic neurologic illnesses, with a significant loss of quality of life.

Parkinson’s disease (PD) represents a major public health concern, affecting 1% of European populations. PD is found throughout the world in all races. It affects males and females about equally or with a slight male predominance. Prevalence of PD is age related with 1.4% of population over age 55 and 3.5% of population over age 75 being affected. As the life expectancy is increasing and in India too, aging population above 60 yrs has been estimated to be almost double from 7.7% in 2001 to 12.30% in 2025. Thus age related neurological disorder may increase at alarming rate. A review from India in 2003 had suggested a low prevalence of PD compared with the rest of the world, except in the Parsi community but now cases are rising and it affects about 8-9 lakh patients in India every year.

There have been many landmark discoveries in PD. In1817; James Parkinson was first to describe the characteristics combination of asymmetrical rigidity, tremor and postural instability, based on his observations as a general practitioner in East London. Pathologically, in 1895 Brissaud implicated the midbrain, observing that “a lesion in the locus nigter could reasonably be the anatomical basis of Parkinson’s disease”, whereas Birk-mayer and Hornykiewicz discovered the therapeutic benefits of L-dopa in1961.

Clinical Features

Common signs on clinical examination include decreased facial expression (masked faces), decreased eye blinking (reptilian stare), resting tremor, and rigidity. The classic tremor is 4-6 Hz at rest, although it may be absent in one quarter of the cases of PD. In addition patient may show disturbance in gait, impaired speech, muscle weakness and autonomic hyperactivity like salivation and seborrhea. Rigidity can be cogwheel (catch-and-release) or lead-pipe (continuously rigid). Other signs include flexed posture, shuffling gait, retropulsion, freezing of gait, decreased olfaction, and micrographia. Myerson’s sign is the inability to resist blinking when the glabella (area above the nose and between eyebrows) is tapped with finger; it can be seen early in PD.

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Of the cardinal signs of PD, akinesia is perhaps the most disabling. Slowness, difficulty in initiation, reduction in amplitude and amount of voluntary movement characterizes akinesia. A lack of facial expression attended by reduced blink rate is one of the most apparent manifestation of akinesia. Additional findings are difficulty arising from a chair, a slow stepped, short stepped gait (low, dragging one foot, steps short, loss of arm swing), and soft articulated speech (hypophonia). The clinical signs of akinesia are so striking that their presence alone has been considered by some to be sufficient to establish a diagnosis of PD. The extrapyramidal symptoms of PD are associated with autonomic symptoms i.e. obstipation, erectile dysfunction, depression and bradyphrenia. Dementia is now recognized as one of the cardinal, non motor manifestation of PD. It is a major cause of disability and unlike the motor manifestations there currently is no effective symptomatic treatment. Farsland and coworkers identified dementia in 28% patients. Neuropsychiatric disturbances- including mood and anxiety disorders, fatigue and apathy, psychosis, cognitive impairment, sleep disorders and addictions which can be part of the process of PD itself, or may result from complex interactions between the progressive and widespread pathologic changes of the disease, emotional reactions to Parkinsonism, and treatment-related side-effects. More than 60% of patients with Parkinson's disease report one or more psychiatric symptoms at some point in the course of their illness. These symptoms are often a significant source of disability and constitute some of the most difficult treatment challenges in advanced Parkinson’s.

However, the average duration of time for the disease to take a worse course, is around ten to fifteen years. The early symptoms are often interpreted as aging, musculoskeletal problems or other systemic illness. Death may occur in extreme case from bronchitis, but more commonly, after the lapse of many years, the patient becomes bedridden from increasing weakness and rigidity and sinks into a condition of sleepiness which is soon followed by coma.

**Etiology**
The etiology of idiopathic PD remains unknown, although environmental and genetic factors (or a combination of the two) are considered to play a role in the development of the disease. PD has been associated with exposure to number of environmental agents, including pesticides, herbicides, metals, and well-water consumption. Beside this, oxidative stress, aging, environmental toxins, mitochondrial dysfunction, neuronal loss, excitotoxicity, neurotrophic factors, immune factors and genetic factors (Synuclein and Parkin) have been found to be associated with pathogenesis of PD. The detailed description of the role, these factors play in pathological cascade of PD is beyond the scope of present review.

**Pathophysiology of PD**
The brain consists of areas of gray matter and white matter. The white matter consists of tightly packed intermingling bundles of axons carrying messages to, from and within the brain. Many large and small clusters of nerve cells are also located in areas directly in the white matter. One such cluster located in the centre of white matter, on each side of the brain is called basal ganglia. Parkinson’s disease is caused by the death of nerve cells in basal ganglia, particularly substantia nigra, the part involved in coordinating movement. These cells communicate with other cells in the nervous system through a chemical called dopamine, which is a neurotransmitter. The shortage of dopamine that results from the loss of these cells causes a debilitating tremor and rigidity of the muscles. Actually, the loss of dopamine means that even if someone knows what to do, the muscles will fail to respond to his intentions. Damage to the dopamine containing cells by lewy bodies can only be detected by examination of the brain under a microscope after a person has died. At birth, the nigra contain about 400,000 dopaminergic cells, falling to 250,000 by the age of 60. There is a parallel loss of dopamine in the striatum. (Carlsson,1976) When the cell population or dopamine content reaches 20% of youthful age signs of Parkinson appear.

Dopamine in dopaminergic neurons is packaged into vesicles and delivered to the presynaptic membrane where it is released and binds with the dopamine receptors on the postsynaptic targets in the striatum. The loss of dopaminergic neurons leads to a profound deficit in the neurotransmitter dopamine in the striatum. Clinical signs of disease appear when striatal dopamine is reduced by 80%. The mainstay of pathophysiology is progressive loss of neurons in the substantia nigra (SN) with the presence of ubiquinated protein deposits in the cytoplasm of neurons (Lewy bodies) and thread-like proteinaceous inclusions with dopaminergic cell loss in within neurites (Lewy neurites). SN directly leads to dopaminergic deficiency in the substantia nigra pars compacta (SN pc). The pathophysiologic progression is thought to start in the dorsal motor nucleus of the vagus nerve and intermediate reticular region of the medulla, then progressing to SN, and then involving the forebrain and ultimately the neocortex as the disease advances.

**Diagnosis**
No laboratory blood test for PD is currently available. The diagnosis remains mostly a clinical one. Neuroimaging studies are used to exclude other causes of Parkinsonism.

**Drug challenge tests:** Levodopa and apomorphine challenge tests are useful in distinguishing PD from other Parkinsonian syndromes. A positive response favors PD; however, these tests have high false-negative (at least 30%) and high false-positive (20 to 30%) rates.

**Olfaction testing:** This may be useful in differentiating progressive supranuclear palsy and corticobasal degeneration from PD. A significant loss of smell is suggestive of PD rather than other Parkinsonian syndromes.

**Neuroimaging:** MRI is useful in distinguishing PD from multisystem atrophy (MSA). The distinguishing characteristic is putaminal hypointensity on T2-weighted images or putaminal hyperintensity on proton density-weighted images. Fast spin echo (FSE) protocol images may show putaminal abnormalities as well. These are usually much more common in MSA than PD.21 Routine neuroimaging of the brain is rarely helpful in PD.

**Existing Therapies**

**Dopaminergic Drugs**
Levodopa/carbidopa since its introduction by Birkmayer and Hornykiewicz in
1961, levodopa has remained the most effective drug for PD and remains the primary treatment for symptomatic patients. Carbipoda prevents peripheral conversion of levodopa to dopamine by blocking dopa-decarboxylase; thus the combination increases cerebral levodopa bioavailability and reduces the peripheral adverse effects of dopamine (e.g., nausea, hypotension). Levodopa is particularly effective at controlling bradykinesia and rigidity, whereas speech disturbance, impaired postural reflex, and gait instability are less likely to respond. The clinical efficacy often declines after long-term therapy and disabling side-effects appear, most notably motor fluctuations such as the wearing-off or on-off phenomena and dyskinesias.

Dopamine Agonists
These include bromocriptine, pergolide, pramipexole, Cabergoline, ropinirole, and cabergoline. Cabergoline, pramipexole treatment of PD results in fewer motor complications (wearing off, dyskinesias, on-off motor fluctuations) than levodopa treatment. However, they are associated with more frequent adverse effects including hallucinations, somnolence and edema. The American Academy of Neurology recommends that the choice between levodopa and dopamine agonists depends on the relative impact of improving motor disability (better with levodopa) compared to the lessening of motor complications (better with dopamine agonists) for each individual patient with PD. Pergolide and cabergoline (ergot-derived dopamine receptor agonists) were recently found to be associated with significantly increased risk for valvular heart disease and were recalled from the market. Dopamine agonists produce a lower incidence of involuntary movements, which seems to reflect their longer duration of action and supports the concept of continuous dopaminergic stimulation.

Mao Inhibitors & Catechol O-Methyl Transferase (Comt) Inhibitors
Monoamine oxidase inhibitors inhibit dopamine metabolism and have been introduced in the therapeutic armamentarium decades ago, but research on this substance continued bringing along new improvements and possibly a dual (symptomatic as well as neuroprotective) action. Selegeline is currently the most widely used monoamine oxidase-B inhibitor for Parkinson’s disease, but has a low and variable bioavailability, and is metabolized to L-methamphetamine and L-amphetamine that carry a risk for potential neurotoxicity. Rasagiline is a new monoamine oxidase inhibitor, without known neurotoxic metabolites. In large clinical trials, rasagiline proves effective as monotherapy in early Parkinsons disease, as well as adjunctive therapy to levodopa in advanced disease. Inhibitors of catechol-O-methyl transferase (COMT inhibitors) include entacapone, and tolcapone. COMT inhibitors decrease the degradation of levodopa and extend its half-life, thus relieving the end-of-dose wearing-off effect and reducing off time.

Cholinergic Drugs
Both the corticostriatalthalamic loop and the nigro striatal system are largely innervated by cholinergic afferents coming from the tegmentum, the septum and by cholinergic interneurons. Most cholinergic systems are affected in PD, such as muscarinic receptors nicotinic receptors, and choline transporters. Anticholinergics were among the first drugs used in PD, and were intended to correct the imbalance between dopamine and acetylcholine levels. Although these drugs do produce some beneficial effects on PD symptoms, they are associated with adverse cognitive effects. They have mixed effects on motor function. Relevance of use of anticholinergics in PD treatment can be traced form the fact that nicotinic receptors are not only highly expressed on dopaminergic neurons but also in the cortex and thalamus. Nicotine has been found to protect against degeneration in various PD models. Glutamate and Gaba Drugs
Majority of pathways in the basal ganglia utilize glutamate and GABA (-aminobutyric acid) as their respective excitatory and inhibitory neurotransmitters, these systems are obvious drug candidates. Indeed, there is already some evidence that N-methyl-d-aspar-tate (NMDA) receptor antagonists, such as remacemide, amantadine and dextromethorphan, might reduce motor complications associated with L-DOPA therapy.

Serotonergic Drugs
5-HT receptors are crucial to motor control in health. In PD, 5-HT1-A, 5-HT1-B, 5-HT2A and 5-HT2C deserve special attention, particularly with respect to involvement in L-DOPA-induced dyskinesia. In animal models 5HT 1 receptor agonist, sarizotan improved levodopa induced dyskinesia. In clinical trials too, 5HT1-A agonist Sarizoton and busipiron reduced Parkinson symptoms. However, at high doses, sarizotan can exacerbate Parkinsonism. This might reflect an interaction between Parkinsonism with dopamine receptors. Therefore Serotonergic drugs can be thought to be a future drug candidates.

Opioid Drugs
Recognition of the enhanced opioid peptide transmission in the striatum of animal models and PD patients with levodopa induced dyskinesia motor complications has raised the possibility of controlling these by targeting opioid. The use of selective mu- and delta-receptor antagonists, but not of - receptor, however, looks more promising as new therapeutic avenues in PD treatment.

Coenzyme Q10
A recent study of Coenzyme Q10 (CoQ10) supported its possible neuroprotective role in neurodegenerative diseases, including the MPTP model of Parkinsonism.

Treatment Through Exercise/Physiotherapy
The importance of regular exercise can scarcely be overemphasized in Parkinson’s disease. The patient who has only slight slowing of voluntary movement should aim to take a walk of about one mile everyday. In addition, at least once a day, preferably half an hour after the first dose of the day’s treatment, the neck, trunk and limb muscles should be exercised. In this way a loosening up of joints and muscles can be achieved which will tend to counteract pain and stiffness and maintain flexibility. Physiotherapy can also give relief to pain. Physiotherapy means treatment using physical means. These techniques involve exercise, manipulation and the application of heat or other forms of stimulation to inflamed areas. In Parkinson’s disease, physiotherapy can be useful to maintain loose joints and muscles, improve co-ordination and dexterity of the hands to improve posture and increase awareness of the body position.

Treatment Through Brain Grafting
Over the past few years, doctors have tried treating people with Parkinson’s disease by grafting dopamine producing nerve cells into their brains. The cells have to be taken from the brains of aborted fetuses and the first attempts were made in 1981, at Sweden to transplant...
the patients own adrenal medulla (autograft) into the caudate nucleus, a part of the basal ganglia which is involved in the transmission of dopamine. The technique has rarely been successful mainly because around ninety eight per cent of the grafted cells die. Of more than two hundred patients treated around the world, fewer than ten percent have shown significant improvement. Researchers had to use tissues from as many as seven fetuses to provide enough cells for a single graft. The number of operations performed has been very small largely because it involves major surgery and because there are ethical problems concerning the use of foetal donor tissues. Two sources of tissue for brain grafting have been used till date—the adrenal medullary autograft and fetal midbrain.23

Adrenomedullary transplantation showed little efficacy and unacceptable morbidity and mortality while trials with human fetal mesencephalic tissue had more promising results, but failed to show a significant clinical benefit.49

**Treatment Through Reparative Therapy**

Reparative therapy is the application of growth factors that prevent further degeneration and stimulate the function surviving neurons. The first growth factor to be discovered nerve growth factor (NGF) had no effect on dopaminergic neurons. Another neurotrophic factor named as glial cell line derived neurotropic factor (GDNF) prevented the loss of these damaged cells. Hence the result suggests that GDNF could slow the progress of Parkinson’s disease.23

**Surgical Management of PD**

Surgical treatment is becoming increasingly common in PD, mainly due to advances in neuroimaging and neurosurgical techniques.16 Procedures include unilateral pallidotomy or deep brain stimulation (DBS) of the subthalamic nucleus (STN). Deep-brain stimulation of the three overactive nuclei include the region, the thalamus (nucleus ventralis intermedius or Vim) for contralateral tremor; the globus pallidus interna for contralateral rigidity, akinesia and specifically levodopa-induced dyskinesia; and the subthalamic nucleus for all three cardinal symptoms. Complications of surgery or medication are frequent and may decrease the quality of life, despite improvement in motor signs.4

**Gene Therapy in PD**

Until recently, sporadic PD was considered the result from age-related and environmental factors with minimal genetic input.50 By using extended pedigree and familial aggregation studies, a genetic predisposition to sporadic PD has been established, although the extent to which genetics determines the risk for late onset PD remains in question. Gene therapy is another exciting arena and includes both potentially neuroprotective and neurorestorative agents.52 Parkinson’s disease (PD) is a good target for gene therapy because the lesion is localized to the substantia nigra (SN). There are several approaches in gene therapy for PD: For enhancing dopamine production, the candidate genes are tyrosine hydroxylase, AADC and/or GTP cyclohydrolase I and a neuroprotective strategy is based on the usage of genes for neurotrophic factors or anti-apoptotic agents. In 2003, the first gene therapy trial for PD was performed at New York Weill Cornell Medical Center. The treatment was designed to deliver glutamic acid decarboxylase (GAD), the gene responsible for making GABA, into the subthalamic nucleus to “quiet down” that nucleus and alleviate Parkinson’s symptom the last approach is replacement of disease for autosomal recessive PD. Because autosomal recessive juvenile Parkinsonism (ARJP) involves the loss of function of parkin gene, gene therapy employing the parkin gene may prevent nigral cell death.53 Beside all these anti apoptotic agents, anti-apoptotic kinase inhibitors (CEP-1347), modulators of mitochondrial function (eg, creatine), growth factors (eg, leterpinim) neuroimmunophilins (V-10367), estrogens (MITO-4509), c-synuclein oligomerization inhibitors (eg, PAN-408) and sonic hedgehog ligands are the future areas where better results are expected to be delivered.

**Conclusion**

PD is a progressive multicentric neurodegenerative disease involving several neurotransmitter systems. Dopamine-replacement therapies have been highly successful in improving the motor features of the disease but the value of these treatments, particularly l-DOPA, is limited by the development of motor complications. Despite advances in our understanding of PD, and development of new treatment strategies, this disease remains one of the most disabling disorders in the older population. Disease modification remains the most important goal in PD. Although several candidates have shown promise yet no drug has been proven to be neuroprotective and modifying the root cause of disability. Above all scientific community must be patted for the work done till date but still lot of scope is left for better designing of new molecules with maximum benefit for the sufferers.

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