Journal of Pharmaceutical Research Vol. 12, No. 2, April-June 2013 : 39-42.

PARKINSON'S DISEASE: A REVIEW

Fatima Urooj, Niazi Samia Gul, Adil Anam, Akht ar Shahzad [1] and Qadir M Imran *
College of Pharmacy, G.C. University, Faisalabad, Punjab, Zip(pin)code: 38000, Pakistan.
[1]Department of Cardiology, Jinnah Hospital, Lahore, Pakistan.

Received on : 26.07.2012 Revised : 07.05.13 Accepted : 13.05.13

ABSTRACT
Parkinson's disease (motor neuron disease) is a degenerative disorder of the central nervous system. The distinctive physical signs that are involved in Parkinson's disease (PD) are tremor, rigidity, postural instability and bradykinesia. Dopaminergic activity and neurons in the substantia nigra and nigrostatic pathway of the midbrain are lost in case of Idiopathic PD. Some drugs like metoclopramide and haloperidol are involved in case of secondary Parkinsonism. Diagnosis of PD is based on the history of patient and physical findings. Dopamine agonists are considered to be the most effective treatment for Parkinson's disease because they act directly on the dopamine receptors in the brain and help to palliate the symptoms of PD. Other pharmacological treatments include the drugs that inhibit dopamine-metabolizing enzymes (monoamine oxidase-B and catechol *O*-methyltransferase). Surgery may be indicated for some patients or when symptoms do not respond to medical therapy.

Keywords: *Lewy bodies; Dopamine; Substantia nigra.*

INTRODUCTION

In case of PD a progressive deterioration of neurons occurs in substantia nigra. Normally these neurons are involved in production of a neurotransmitter known as Dopamine. Abnormal nerve functioning takes place in case of decreased dopamine secretion, and this causes the loss of ability to control the body movements. The cardinal clinical signs appeared in the PD are rest tremors, bradykinesia, rigidity, loss of postural reflexes, and gait freezing.[1] Prevalence of PD is more common in elder patients and most of the times occur after the age of 50.

EPIDEMIOLOGY

PD is a syndrome that affects both sexes equally but show a minor dominance in males, this disease mostly occurs throughout the world in all native groups.[2] The prevalence of PD is about 0.3 % in the individuals between 65 and 90 years of age, 3% of population shows this disease in the age of 65 years.[3] The incidence of PD is less reported in Asians and African blacks, but high incidence is found in whites. The pervasiveness of Lewy bodies (collection of abnormal proteins that clump together to form a redish-pink cytoplasmic composition in the substantia nigra neurons) in the brains of Nigerian population is similar to that in Western populations. [4] This suggests that the development of PD is broad; and its prevalence in different age groups indicate that environmental factors are also involved with it.

In brain, dietary factors may change the impression of Levodopa action and hence affect the motor performance of the brain. The food that contain high protein can interfere with the absorption of Levodopa.[5]

CLINICAL PRESENTATION

PD is the motor neuron disease and affects the movement, so producing the motor symptoms. But non motor symptoms like autonomic dysfunction, neuropsychiatric, sensory and sleeping disorders are also common.[6] The cardinal clinical signs originate in the PD are mention in Table 1.

Table 1: *Cardinal clinical signs of PD*

CLINICAL SIGNS				
Tremors	***Speech***	***Rigidity***	***Bradykinesia***	***Postural instability***
a) Frequency of PD tremor is between 4 and 6 hertz (cycles per second). b) Rest tremor: maximum when the limb is at rest and disappearing with voluntary movement and sleep.	Pronunciation is initially a monotone but progresses to characteristic tremulous slurring dysarthria.	Uniform (lead-pipe rigidity) or cogwheel rigidity	Difficulties in the whole course of the movement process, from planning to initiation and finally execution of movement	Postural instability leads to impaired balance, frequent falls which may result in bone fractures

ETIOLOGY

Two factors i.e.; genetic and environmental factors have been considered as a cause of the Parkinson's disease, but there is no clear evidence which show the dominance of any one factor.

A) ENVIRONMENTAL FACTORS (MPTP)

Number of toxins induced the neurological disorders that damage the basal ganglia and substantia nigra and produce the features like PD.MPTP is a toxin that in involved to target those neurons that are responsible in PD. In 1980s, environmental factors became more superior when drug addicts accidently produced a toxin called MPTP. Ingestion of or inhalation of MPTP rapidly produced a severe PD. [7]

*Correspondence : urooj21@hotmail.com

B) GENETIC FACTORS

Six genes have been found to be associated with PD. Mutations in these specific genes alpha-synuclein, parkin, UCHL1, DJ1, PTEN induced putative kinase 1 (PINK1), and eucine-rich repeat kinase 2 (LRRK2) induces PD. [8,9] The families which have autosomal recessive PD cases have mutation in parkin gene of chromosome 6. This mutation probably accounts for the PD in the age group below 40 years.[10] Mutations of the alpha-synuclein gene and ubiquitin carboxyl-terminal hydrolase LI (UCHL1), on chromosomes 2pl3 and 4pl4-16.3 respectively, has also reported infrequent cases of Parkinsonism.

PATHOLOGICAL FEATURES

Seriously affected area of the brain in PD is basal ganglia which are innervated by dopaminergic system.[8] The main pathological feature of PD involves death of brain cells. The parts of the brain which are affected the most are substantia nigra and ventral part of compacta, which accounts for 70 % of total cell death in brain. [11]

The macroscopic examination of the cut surface of the brainstem of person suffering from PD has shown neurological loss in substantia nigra and locus coeruleus. [10]

Microscopic (histopathology) studies have shown that the two distinctive features in case of PD; first one is neuronal loss and second one is the clumps of Lewy bodies in substantia nigra and other parts of the brain. Neuronal loss that takes place in PD is due to death of astrocytes and activation of microglia. Main pathological distinctive feature in PD is the Lewy body. [10]

PATHOPHYSIOLOGY

There are five major pathways in the brain- motor, oculo-motor, associative, limbic and orbitofrontal circuits, theses all are connected through basal ganglia.[12] Movement, attention, learning and speaking are the major functions that are carried out by these pathways. All of these pathways perform their role in PD. Main pathway that plays its immense role in PD is the motor pathway. In case of PD all motor activities initiated by the motor pathway is inhibited by basal ganglia.[12]

Dopamine is the key neurotransmitter that is involved in the motor activity, high level of dopamine release play their role in motor functions and if the level of dopamine decreases motor activity is disturbed and PD is developed. So, hypokinesia is produced as a net effect of dopamine depletion, and due to this there is overall reduction in motor activity.[12]

Drugs that are given in PD have dopaminergic activity and these drugs at times activate the motor system at the improper time leading to dyskinesia.

There are different mechanisms in PD where brain cell activity is lost and there is abnormal accumulation of á-syncline protein that is bound to ubiquitin in the damaged brain cell. This protein form the insoluble aggregates that accumulate in the neuron and produce the inclusion bodies that are known as Lewy bodies. When disease progresses Lewy bodies spread in substantia nigra and basal forebrain and at the end in neocortex. In the later stages of the disease theses sites of brain are involved in neuronal degeneration.[12-14]

DIGNOSIS

In PD the progressive degeneration of pigmented neurons in the substantia nigra leads to a deficiency of the neurotransmitter Dopamine. The characteristic sign and symptoms of this disease are produced when there is a neurochemical (dopamine) imbalance in the basal ganglia. Drug therapies in these cases do not prevent the disease progression but it improves the quality of life of patients. Patients with suspected PD should be referred to a specialist to confirm the diagnosis; the diagnosis should be reviewed every 6-12 months. Hallmark resembling those with PD can also occur in disease such as PSP and MSA, but they don't normally show a confirm response to the drugs used in treatment of PD.[15] In Table 2, we concluded how to differentially diagnose the PD.[15-17]

Table 2: *Differential diagnosis of PD*

Differential Diagnosis of PD			
Disease	***History of Patient***	***Distinguish features***	***Best Diagnosis***
Idiopathic Parkinson's disease	Gradual onset, tremor, gait disturbance, slower movements	Resting Tremor (mostly affects the limbs than the head) Cogwheel rigidity (mostly affects the limbs than the neck and spine)	Physical examination.
Drug-induced parkinsonism	Exposure to dopamine-blocking drugs	Same as in Idiopathic PD	Patient history and Physical examination.
Multisystem atrophy (MSA)	Parkinsonism with autonomic disturbance, early gait instability, dysphagia	Orthostatic hypotension, skin changes (e.g., seborrhea, relative absence of tremor	Physical examination.
Essential tremor(ET)	Present for many years, positive family history	Tremor with arms raised (postural), head involved.	Physical examination. Tremor is the only and predominant feature.
Huntington's disease	Involuntary movements, cognitive or behavioral problems	Chorea, loose tone, early dementia	CT or MRI studies of head to measure caudate nuclei
Multiple lacunar strokes	Stepwise neurologic complaints and functional loss	Focal findings, asymmetric sensory or motor loss	CT or MRI studies of head
Pugilistic (post-traumatic) parkinsonism	Repeated head trauma	Bradykinesia, evidence of previous trauma	CT or MRI studies of head
Progressive supranuclear palsy (PSP)	pseudobulbar affect, early gait instability, dysphagia	Supranuclear downgaze palsy, square-wave jerks, upright posture.	CT or MRI studies of head

CT = computed tomography; MRI = magnetic resonance imaging

Pharmacological T reatment

Before initiating the therapy patient should be advised about limitations and possible side effects of that medication. About 5-10% of patients with PD respond poorly to therapy. Therapy is usually not started until symptoms cause significant disruption of daily activities. Therapy with two or more antiparkinsonian drugs may be necessary as the disease progresses. Antiparkinsonian drug therapy should never be stopped

abruptly because this carries a small risk of neuroleptic malignant syndrome.

Antiparkinsonian drugs can cause confusion in elderly. It is particularly important to initiate the therapy with low doses and increase it gradually.[15] Table 3 summarize the pharmacological treatment of PD. [18-20]

Table 3: *Pharmacological Treatment of PD*

Pharmacological Treatment of Parkinson's Disease					
Drug	***Mechanism of action***	Indication	Side effects	Dosage	Contra -indications
Increase dopamine levels					
Levodopa Carbidopa	Stimulate the dopamine receptors	PD	Dizziness, nausea, hallucinations and others	25/100 mg three times daily	Pregnancy, breast feeding
Amantadine	Dopamine reuptake inhibitor	PD	Confusion, nausea, hallucination	100 mg twice daily	Epilepsy, history of gastric ulcer, renal impairment, pregnancy
Pramipexole	Dopamine agonist (receptor stimulation)	PD	Hypotension, Dizziness,dyskinesia, hallucinations.	0.125 mg three times daily	Breast feeding
Bromocriptine	Dopamine agonist (receptor stimulation)	PD	Hypotension, Dizziness,dyskinesia.	1.25 mg twice daily at night.	Hypersensitivity to bromocriptine or other alkaloids,toxaemia of pregnancy and hypertension in postpartum women.
Ropinirole	Dopamine agonist (receptor stimulation)	PD	Hypotension, Dizziness, dyskinesia,syncope.	0.25 mg three times daily	Breast feeding and pregnancy.
Pergolide	Dopamine agonist (receptor stimulation)	PD	Abdominal pain, dyskinesia, hallucinations.	0.05 mg at night	History of fibrotic disorders, cardiac valve disease
Inhibit dopamine metabolism					
Selegiline	MAO-B inhibitor	PD(used alone or as an adjunct to levodopa with dopa-decaboxylase inhibitor)	Insomnia, headaches, sweating, confusion	5 mg twice daily	Pregnancy, breast feeding
Rasagiline	MAO-B inhibitor	PD(used alone or as an adjunct to levodopa with dopa-decaboxylase inhibitor)	Dry mouth, dyspepsia, constipation, depression.	1mg daily	Pregnancy, breast feeding
COMT Inhibitors					
Tolcapone	COMT inhibitor	PD	Dizziness, orthostasis, diarrhea	100 mg three times daily	Hepatic impairment,phaeochromocytoma,rhabdomyolosis.
Entacapone	COMT inhibitor	PD	Drowsiness, dry mouth, blurred vision,fatigue	200mg with each dose of levodopa with dopacarboxylase inhibitor, max.2g daily	Hepatic impairment,phaeochromocytoma,rhabdomyolosis,pregnancy.
Antimuscarinic Drugs					
Procyclidine Hydrochloride	Anticholinergic activity	PD	Confusion, dry mouth, nausea	2.5mg 3 times daily	Avoided in gastro-intestinal obstruction and myasthenia gravis

MAO= monoamine oxidase , COMT= catechol O-methyltranferases

Controlled release Carbidopa/Levodopa and immediate release Carbodopa/Levodopa are evenly efficacious in treating the symptoms of PD. In the treatment of PD immediate release tablets of Carbidopa/Levodpa gives the highest level of motor function. Carbidopa/ Levodopa combination improves the motor symptoms within half an hour of taking the first dose.

Some patients prefer the controlled release formulation of Carbidopa/Levodpa because they reduce the frequent dosing and longer duration of action.[21]

The adenosine A(2A) receptor agonist Regadenoson is a coronary vasodilator. It has a maximal hyperemic action that stands for an optimal duration. It has 2-3 minutes half life. The evaluation of A(2A) are under clinical trial (Phase I to III) to treat the PD. It is concluded that A(2A) Regadenoson can be used in combination with L-DOPA to denigrate the motor symptoms of PD.[22]

REFERANCE

1. Carl Clarke, Tara Sullivan, Alastair Mason, David Burn. National Institute for Health and Clinical Excellence. Parkinson's disease: Diagnosis and management in primary and secondary care. London: Royal College of Physicians. June 2006, pp 4-5.
2. Zhang Z-X, Roman GC. Worldwide occurrence of Parkinson's disease: an updated review. Neuroepidemiology. 1993;12:195-208.
3. Moghal S, Rajput AH, D'Arcy C, Rajput R. Prevalence of movement disorders in elderly communityresidents. Neuroepidemiology. 1994; 13:175-178.
4. Jendroska K, Olasode BJ, Daniel SE, Elliott L, Ogunniyi AO, Aghadiuno PU, Osuntokun BO, and Lees AJ. Incidental Lewy body disease in black Africans. The Lancet. 1994; 344: 882-883.
5. Jean Pintar Hubble and Richard C Berchou. Parkinson's Disease Medication. National Parkinson's Foundation Inc. Dietary consideration.1996-99, pp 71.
6. Ankovic J. Parkinson's disease:Clinical features and diagnosis. J Neurol Neurosurg Psychiatr. 2008; 79 (4): 368–76.
7. Goodwin BL, Kite GC. Environmental MPTP as a factor in etiology of Parkinson's disease. J Neural Transim. 1998; 105 (10-12) 1265-9.
8. Davice CA. A review of Parkinson's disease. Br Med Bull. 2008; 86:109-27.
9. Schapira AH. Etiology of Parkinson's Disease: Neurology. Department of Clinical Neuro-sciences, University College London, United Kingdom. 2006; 66(10 Suppl 4):S10-23.
10. Obeso JA, Rodríguez-Oroz MC, Benitez-Temino B, Blesa FJ, Guridi J, Marin C, and Rodriguez M. Functional organization of the basal ganglia: therapeutic implications for Parkinson's disease. Mov Disord. 2008; 23(Suppl 3): S548–59.
11. Dickson DV. Neuropathology of movement disorders. In Tolosa E, Jankovic JJ. Parkinson's disease and movement disorders. Hagerstown, MD: Lippincott Williams & Wilkins. 2007, pp 271–83.
12. Obeso JA, Rodriguez-Oroz MC, Goetz CG, *Marin C, Kordower JH, Rodriguez M, Farrer M, Schapira AH, and Halliday G.* "Missing pieces in the Parkinson's disease puzzle". Nat Med. 2010; 16 (6): 653–61.
13. Schulz-Schaeffer WJ. The synaptic pathology of alpha-synuclein aggregation in dementia with

Lewy bodies, Parkinson's disease and Parkinson's disease dementia. Acta Neuropathol. 2010; 120 (2): 131–43.

14. McKeith IG, Galasko D, Kosaka K, Perry EK, Dickson DW, Hansen LA, Salmon DP, Lowe J, Mirra SS, Byrne EJ, Lennox G, Quinn NP, Edwardson JA, Ince PG, Bergeron C, Burns A, Miller BL, Lovestone S, Collerton D, Jansen EN, Ballard C, Wilcock GK, Jellinger KA and Perry RH. Consensus guidelines for the clinical and pathologic diagnosis of dementia with Lewy bodies (DLB): report of the Consortium on DLB internationalworkshop. Neurology. 1996;47:1113-1124.

15. British National Formulary, Royl Pharmaceutical Society of Great Britain, British Medical Association. September 2011; 60: 295.

16. Rajput AH, Rozdilsky B, Rajput A. Accuracy of clinical diagnosis in parkinsonism - a prospective study. Can J Neurol Sci. 1991;18:275-278.

17. Hughes AJ, Daniel SE, Blankson S and Lees AJ. A Clinicopathologic study of 100 cases of Parkinson's disease. Arch Neurol. 1993; 50(2): 140-148.

18. Koller W, Pahwa R. Treating motor fluctuations with controlled-release levodopa preparations. Neurology. 1994; 44 (7suppl 6): S23–S28.

19. Münchau A, Bhatia K P. Pharmacological treatment of Parkinson's disease: J Postgrad Med. 2000; 76:602-610.

20. Verhagen Metman L, Del Dotto P, van den Munckhof P, Fang J,Mouradian MM, Chase TN. Amantadine as treatment for dyskinesias and motor fluctuations in Parkinson's disease. Neurology. 1998; 50:1323-1326.

21. Jean Pintar Hubble and Richard C Berchou. Parkinson's Disease Medication. National Parkinson's Foundation, Inc. Levodopa- still the Gold Standard.1996-99, pp 70-79.

22. Armentero MT, Pinna A, Ferre S, Lanciego JL, Muller CE and Franco R. Past, Present and future of A(2A) adenosine receptor antagonist in the therapy of Parkinson's disease. Pharmacol Ther. 2011; 132(3) : 280-299.