Ann Natl Acad Med Sci (India), **44(2):** 139-149, 2008

Parkinson's Disease: Not just TRAP

Madhuri Behari
Department of Neurology, All India Institute of Medical Sciences,
New Delhi-110029

Abstract

James Parkinson described Parkinson's Disease (PD) as a purely motor disorder of progressive stoop, shuffling of gait, tremors and slowness. Over the years some motor and non-motor problems faced by patients PD are being recognized. The main motor features of PD include resting tremor (T), cogwheel rigidity (R), akinesia or bradykinesia (A) and postural instability with gait disturbance (P). The acronym for these motor features can therefore be conveniently called as TRAP. The major problems faced by patients of PD are sleep, problems, neuropsychiatric problems, cognitive impairment, dysautonomia, sensory symptoms, motor fluctuations and dyskinesia and maintenance of balance. A systematic study of some of these problems provides an insight into the morbidity of PD patients which are beyond the symptoms encompassed by TRAP and affect quality of life.

Keywords: Parkinson's disease, resting tremor, cogwheel rigidity, akinesia, postural instability

Introduction

Parkinson's disease is the second common neurodegenerative disorder. The prevalence varies widely in different ethnic groups. On an average it varies from $100/10^6$ to $300/10^6$

Correspondence: Prof. Madhuri Behari, FAMS, Dept. of Neurology, All India Institute of Medical Sciences, New Delhi-110029. Phone: 91-11-26594856, Fax: 91-11-26588166, Email: madhuribehari@hotmail.com. Gen. Amir Chand Oration, 2006-2007. Delivered at the Annual Conference of the National Academy of Medical Sciences (NAMSCON, Amritsar), 2007.

population. Since its first description about two centuries ago by James Parkinson, new symptoms are being increasingly identified which bother the patients (1). James Parkinson described it as a purely motor disorder of progressive stoop, shuffling of gait, tremors and slowness. Over the years some motor and non motor problems faced by patients of Parkinson's disease (PD) are being recognized. The cardinal motor features of PD include resting tremor (T), cogwheel rigidity (R), akinesia or bradykinesia (A) and postural instability with gait disturbance (P). The acronym for these motor features can therefore be conveniently called as TRAP. This also describes very aptly the condition of the patients who seem to be trapped in an immobile rigid body. The standard therapy for PD is based on dopaminergic replacement using dopamine precursor levodopa or dopamine agonists. Typically these provide satisfactory control over motor symptoms in the early stage of the disease. Many patients, however, experience disability despite dopaminergic therapy because of drug related motor complications and emergence of non motor features such as autonomic disturbance, speech and sleep disturbance, gait disturbance and falls, psychosis and dementia. These non motor disturbances are believed to be result of involvement of non dopaminergic neurons in the progressive neurodegeneration which characterizes PD. Further, dopaminergic therapy does not prevent progression and natural course of the disease.

In a very elegant study Braak and colleagues studied brains of PD patients in different stages of disease and individuals who did not have PD. They were able to recognize six stages in which PD could be classified (2). According to Braak's staging, stage 1, is characterized by involvement of lower brainstem and the olfactory area, stage 2 with spread of pathology to the more rostral area into the pons especially locus coeruleus, raphe nucleus and reticular formation. In these two stages the motor symptoms do not appear, but non motor symptoms such as impaired olfaction, constipation and sleep disturbance occur in this stage. In stage 3, the pathological process spreads further rostrally to involve mid brain (subtantia nigra (SN), amygdala, central sub nucleus of forebrain and nucleus of Meynert). It is in this stage when SN pars compacta is affected that the motor symptoms appear. In stages 4, 5 and 6 there is progressive involvement of mesocortex of temporal lobes, Ammon's horns, cingulate and

insular cortex, entero-rhinal cortex and autonomic, limbic and somatomotor areas. This forms the basis of symptoms and signs pertaining to sense of smell, autonomic nervous system, cognition, sleep, depression, anxiety, psychosis and sensory system. The problems of postural instability and falls appear later on in the illness and affect quality of life and adversely affect morbidity and mortality. Some of these problems faced by the PD patients were systematically studied by us providing an insight into the morbidity of PD patients which are beyond the symptoms encompassed by TRAP and affect quality of life.

Sleep problems

Virtually all patients with Parkinson's disease have sleep problems which usually starts early on in the disease (3). The causes are multifactorial including pathological degeneration of central sleep regulation centres in the brainstem and thalamo-cortical pathways (4), motor problems, pain, frequent urination etc. Several sleep problems are reported in patients with Parkinson's disease. These are: sleep fragmentation, excessive day time sleepiness, REM sleep behaviour disorder, paroxysmal limb movement of sleep, and restless leg syndrome. In a prospective study we investigated sleep problems in 149 PD patients and compared it with age matched controls. Sleep problems were reported by 42% of patients compared to 12% among controls (5). Common problems were insomnia (32%), nightmares (32%), excessive day time sleepiness (15%) and RLS (14%). Sleep problems were seen more often in patients with advanced disease, higher disability, higher levodopa dose, and higher rigidity score. Restless leg syndrome, characterized by desire to move legs occurring in late evenings and night, improving with movement of legs and walking is characteristically described as a disorder of dopamine deficiency and responds to dopaminergic agents. These were shown to be 10 times more frequently reported by PD patients as compared to age and gender matched healthy controls (6). REM sleep behaviour disorder (RBD) occurs in about a third of PD patients. It is a parasomnia characterized by loss of normal skeletal muscle atonia during REM sleep resulting in patient physically enacting their dreams. Patient may vocalize, move their limbs or even fall out of bed. It may precede motor symptoms in about 40% of PD patients (7). It is speculated that RDB arises due to degeneration of lower brainstem nuclei including peduculo-pontine and sub-coeruleal nucleus.

Excessive day time sleepiness (EDS) affects up to 50% of PD patients (8). It could be due to poor quality nocturnal sleep or dopaminergic drugs. It rarely may cause sudden onset sleep ("sleep attacks") with motor vehicular accident. This is associated with short sleep latency (<5min) and transition from wakefulness to sleep stage 2 occurring within seconds, similar to narcolepsy. In a study involving 149 PD patients in different stages of illness we observed EDS in 26% of the PD population. It was not a special feature of any drug (9). The suprachasmatic nucleus regulates sleep-wakeful cycle, but its involvement in Parkinson's disease is not proven.

Neuropsychiatric problems

The neuropsychiatric disturbances form important non motor symptoms in PD and range from anxiety, depression and apathy to psychosis. Psychosis is the main reason prompting placement in nursing home in western countries.

Anxiety and Apathy:

Anxiety disorders are common in PD and occur in all stages. When seen in early stage it can be an important preclinical risk factor. In late stages it is usually related to drug induced motor fluctuations. It varies in severity from very mild to severe panic attacks. Apathy has been identified as a distinctive symptom in PD and is indicative of neuro-degenerative process (10). Involvement of frontal subcortical areas and areas between ventral tegmentum and nucleus accumbens is implicated in development of apathy. These symptoms do not respond so well to dopamine replacement therapy indicating involvement of more extensive neurotransmitter pathways.

Depression:

Depending on criteria used depression can affect 10-45% of PD patients (11). Serotonergic as well as limbic non adrenergic and dopaminergic pathways are implicated in its causation. Low levels of 5 HIAA and $5HT1^A$ levels are observed in CSF of depressed PD patients as compared to non depressed patients, supporting the role of serotonergic involvement (12). Characteristic features of depression in PD are low self esteem, feeling of guilt, sadness and remorse. Depression can precede motor symptoms of PD supporting Braak's hypothesis. Suicides are rare though suicidal ideations are common. Depression in PD is a significant determinant of quality of life.

Psychosis and hallucinations:

Up to 40% of PD patients have hallucinations especially in advanced

stage. In most of these, the hallucinations are benign. More sinister symptoms such as delusions, paranoid ideation and delirium are not so common. Though often the hallucinations are visual, occasionally auditory hallucinations may also occur. Visual hallucinations are usually due to the drugs but degeneration of pedunculopontine nucleus, locus coeruleus and dopaminergic raphe nucleus are also implicated (13). Risk factors for hallucinations are use of dopa agonists, cognitive impairment and old age. According to one hypothesis, sleep fragmentation leads to vivid dreams, hallucinations and delirium. Some studies have shown polymorphism in cholecytokinin gene in PD patients with hallucinations (14). Psychosis and hallucinations are an important cause of placement in nursing home in western countries and are an important cause of care giver burden.

Cognitive impairment:

Though frank dementia occurs in only about 40% people with PD, subtle cognitive impairment in terms of neuropsychological examination is observed in almost all patients (15). Dementia is progressive and is characterized by dysexecutive syndrome with impaired visuo-spatial ability and memory impairment. The causative factors are degeneration of nigral cells, presence of cortical lewy body and loss of cholinergic cells in nucleus basalis of Myenert. In addition, other co-morbidity like Alzheimer's disease, vascular pathology and APoE genotype may also be contributory factors.

Dysautonomia:

Though prominent dysautonomia is a feature of multiple system atrophy (MSA), early and subtle involvement of autonomic functions are observed in PD and are due to involvement of dorsal nucleus of vagus, nucleus ambiguus, and other medullary centers (2). Additionally, degeneration of cholinergic mono-aminergic and serotonergic nuclei leads to abnormalities in modulation within central autonomic system. In a study almost 50% of PD patients reported their symptoms of autonomic disturbance as highly disabling (16). Cardiac MIBG imaging shows early cardiac sympathetic denervation in PD and not MSA. Whereas, postural hypotension, sweating disturbance etc. occur late in PD, constipation is a prominent symptom seen even before motor symptoms appear. Although there is severe loss of dopaminergic neurons in the colon, constipation does

not respond to dopaminergic treatment suggesting role of non-dopaminergic mechanism. Additionally sexual dysfunction is also reported. Aberrant sexual behaviour and drive are especially features of dopamine dysregulation syndrome (17). Disturbance of sweating is also a major problem in PD especially during off phase. This problem was studied by us using electrophysiological methods of sympathetic response. We observed a large number of patients with abnormal sympathetic skin response suggesting peripheral involvement of sympathetic fibres (18).

Sensory symptoms:

Sensory symptoms such as pain are especially prominent symptoms in patients with PD who develop off periods and dystonias (19). "Frozen shoulder" due to painful restriction of shoulder movements is often the first symptom in PD especially if it starts in an upper limb. Impaired olfactory function is being recognized as a preclinical marker of PD. It gains support from Braaks' hypothesis according to which in stages 1 and 2 the olfactory bulb and anterior olfactory nucleus are predominantly affected. In a study involving 361 asymptomatic relatives of PD patients, 40 were identified to have hyposomnia of which 10% developed PD in 2 years and another 12% showed presynaptic abnormality on SPECT scan. None of the relatives with normal smell sensation developed PD or abnormal SPECT scan (20). It is also seen that hyposomnia like RBD is a marker of synucleopathy (such as PD, diffuse Lewy body disease and multiple system atrophy) and is not seen in other disorders in which parkinsonism is a feature such as progressive supra-nuclear palsy and cortico-basal ganglion degeneration.

Motor fluctuations and dyskinesia:

Early in the course of PD, levodopa controls the primary motor symptoms and provides smooth relief for almost all patients. Initially the effect of a single dose of levodopa lasts for more than 4 hours. Over the years, the drug fails to provide these relatively long symptom free period and patients experience "wearing off", "on" and "off" phenomenon. In some patients in advanced stage there is "delayed on" or "on-on" as well. In addition some patients develop periods of involuntary choreic movements (levodopa induced dyskinesia) characterized by twisting and turning. These may occur when the peak effect is on or during "off" phase. In advanced PD patients these motor phenomenon may be more disabling

than the symptoms of PD itself. Though levodopa is the gold standard in the treatment of PD more than half the patients develop dyskinesia after 5 years of disease. The patients also experience a shorter duration of symptom relief. The literature suggests that motor complications in PD are related to progression of disease and pulsatile non-physiological stimulation of dopamine receptors (21). These result in molecular and physiological changes in receptors resulting in motor complication. In ELLDOPA and CALM-PD trials it was observed that patients initially started on dopamine agonists with longer duration of action and non-pulsatile stimulation of dopaminergic receptors developed dyskinesia much later as compared to patients started on levodopa right in the beginning (22,23). Table 1 shows incidence of motor fluctuations as observed by some authors. Obesso and colleagues presented a classification scheme of PD in which an early stage (3-5 years) is characterized by good response to levodopa, an intermediate stage (5-10 year) in which approximately 50-70% of patients suffer from some drug related motor symptoms and an advanced stage (more than 10 year) when motor complication impair quality of life (29).

Table 1 : Levodopa induced dyskinesia as observed by various authors.

Author	Fluctuations (Wearing off)	Dyskinesia	Duration Years
Rajput *et al* (1984)(24)	10%	25%	5
Poewe *et al* (1986)(25)	52%	54%	6
PSG (1996)(26)	50%	30%	2
Denny and Behari (1999)(28)	27%	25%	—
PSG (2000)(23)	—	30%	2
Rascol *et al* (2000)(27)	45%	—	5

Maintenance of Balance and Falls:

Falls are major problems in patients with Parkinson's and are responsible for major morbidity and mortality. As compared to age matched healthy individuals, patients with PD fall about twice as often (30% vs. 60%) (30). Several causes of falls are identified, such as muscle weakness, sensory abnormality, extrapyramidal

dysfunction and postural instability. Though PD patients complain of weakness, objective isometric muscle strength testing is not performed in many studies. Isometric, isokinetic and torque testing have shown impaired velocity and strength of muscles (31). Impaired righting reflexes are also important in falls resulting in fracture neck of femur in contrast to wrist fracture in healthy controls. Somato-sensory functions especially proprioception is also impaired in PD patients resulting in misjudgment of extent of movements (32).

In a comprehensive study we assessed the motor and sensory organization of PD patients during "on" and "off phase" in a quantitative manner to study the role of each of these factors and the effect of drugs (33). The sensory organization test done with eyes open, eyes dosed, altering proprioception, and sway vision showed significant difference between the controls and patients, both during "off" phase and "on" phase, especially on test of proprioception, sway vision, and eyes open-sway support indicating that though vestibular function is not impaired proprioception is impaired in PD patients. Tests of limits of stability showed significant difference on maximum velocity, directional control, maximum excursion and end point excursion between controls and PD patients.

The dynamometer assessment of peak torque also showed significant difference between PD patients and controls in both "on" and "off" periods. The test of gait which measured, base, cadence, stride length, step length and velocity also showed highly significant difference between the PD patients and controls. We also observed that antiparkinsonism drugs have little effect on all these functions except dynamic motor functions. It showed that both motor and sensory functions are impaired in PD patients. The basal ganglion functions as central integration of motor and sensory functions. The supplementary motor area, well connected with the basal ganglion plays a major role in motor planning. Studies on MPTP treated parkinsonian monkeys suggest impairment of cortical processing of sensory information (34). In another study using clinical tests, among 102 PD patients we observed that 35% of PD patients were fallers, and predictors of falls were longer duration of PD, presence of motor blocks, freezing of gait, dyskinesia, duration of "off" period and fear of falls.

References

1. Parkinson J (2002). An essay on the shaking palsy (reprint of monograph published by Sherwood, Neely and Jones. London 1817). *J.Neuropsychiatry Clin Neurosci* **14**:223-36.
2. Braak H, Del Tredici K, Rub U, de Vos RAI, Jansen Steur ENH, Braak E (2003). Staging of brain pathology related to sporadic Parkinson's disease. *Neurobiol Aging* **24**:197-210.
3. Chaudhuri KR (2003). Nocturnal symptom complex in PD and its management. *Neurology* **61(Supp 3)**: S17-S23.
4. Shouse MN, Siegel JM (1992). Pontine regulation of REM sleep components in cats: integrity of the pedunculopontine tegmentum (PPT) is important for phasic events but unnecessary for atonia during REM sleep. *Brain Res* **571**:50-63.
5. Kumar S, Bhatia M, Behari M (2002). Sleep disorders in Parkinson's disease. *Movement Disorders* **17 (4)**: 775-781.
6. Krishnan PR, Bhatia M, Behari M (2003). Restless legs syndrome in Parkinson's disease: A case controlled study. *Movement Disorders* **18(2)**:181-185.
7. Schenck CH. Bundle SR, Mahowald MW (1996). Delayed emergence of a parkinsonian disorder in 38% of 29 older men initially diagnosed with idiopathic rapid eye movement sleep behavior disorder. *Neurology* **46**:388-93.
8. Abbott RD, Ross GW, White IR *et al* (2005). Execessive daytime sleepiness and the future risk of Parkisnon's disease. *Mov. Disord* **20(Suppl 10)**:S101.
9. Kumar S, Bhatia M. Behari M (2003). Excessive daytime sleepiness in Parkinson's disease as assessed by Epworth Sleepiness Scale (ESS). *Sleep Medicine.* **4(4)**: 339-342.
10. Weisskopf MG, Chen H, Schwarzchild MA, Kawachi I, Ascherio A (2003). Prospective study of phobic anxiety and risk of Parkinson's disease. *Mov Disord* **18**:646-651.
11. Burn DJ (2002). Beyond the iron mask: towards better recognition and treatment of depression associated with Parkinson's disease. *Mov Disord* **17**:445-454.
12. Doder M, Rabiner EA, Turjanski N, Lees AJ, Brooks DJ (2000). Brain serotonin 5HTA receptors in Parkinson's disease with and

without depression measured by positron emission tomography with 11CWAY 10635. *Mov.Disord* **15**:213.

13. Diederich NJ, Goetz CG, Stebbins GT (2005). Repeated visual hallucinations in Parkinson's disease as disturbed external/ internal perceptions: focused review and a new integrative model. *Mov.Disord* **20**:130-140.
14. Goldman JG, Goetz CG, Berry-Kravis E. Keurgans S, Zhou L (2004). Genetic polymorphisms in Parkinson disease subjects with and without hallucinations: an analysis of the cholecystokinin system. *Arch Neurol* **61**:1280-84.
15. Emre M (2003). Dementia associated with Parkinson's disease. *Lancet Neurol* **2**:229-37.
16. Magerkurth C, Schnitzer R, Braune S (2005). Symptoms of autonomic failure in Parkinson's disease: prevalence and impact on daily life. *Clin Auton Res* **15**:76-82.
17. Pezzella FR, Colosimo C, Vanacore N *et al* (2005). Prevalence and clinical features of hedonistic homeostatic dysregulation in Parkinson's disease. *Mov Disor* **20**:77-81.
18. Srivastava S, Behari M, Bhatia M (1998). Sympathetic skin response in early Parkinson's disease. *Neurology India* **46** (Suppl 1):
19. Waseem S, Gwinn-Hardy K (2001). Pain in Parkinson's disease: Common yet seldom recognized symptom is treatable. *Postgrad Med* **110**:33-40.
20. Montgomery EB Jr., Baker KB, Lyons K *et al* (1999). Abnormal performance on the PD test battery by asymptomatic first degree relatives. *Neurology* **52**:757-62.
21. Pahwa R, Lyon KE (2004). Options in the treatment of motor fluctuations and dyskinesias in Parkinson's disease: a brief review. *Neurol Clin* **22**:S35-S52.
22. Barone P (2003). Clinical strategies to prevent and delay motor complications. *Neurology* **61(Suppl 3)**: S12-16.
23. Parkinson Study Group (2000). A randomized controlled trial comparing pramipexole with levodopa in early Parkinson's disease: design and methods of CALM-PD study. *Clin Neuropharmacol* **23**:34-44.
24. Rajput AH. Stern W, Laverty WH (1984). Chronic low-dose levodopa therapy in Parkinson's disease: an argument for delaying levodopa therapy. *Neurology* **34**:991-6.

25. Poewe WH, Lees AJ, Stern GM (1986). Low-dose L-dopa therapy in Parkinson's disease: a 6-year follow-up study. *Neurology* **36**:1528-30.

26. Parkinson study group (1996). Impact of deprenyl and tocopherol treatment on Parkinson's disease in DATATOP patients requiring levodopa. *Ann Neurol* **39**:37-45.

27. Rascol O, Brooks DJ, Korczyn AD, De Deyn PP, Clarke CE, Lang AE (2000). A five year study of incidence of dyskinesia in Patients with early Parkinson's disease who were treated with ropinirole or levodopa. *N Engl J Med* **342**:1484-91.

28. Denny AP, Behari M (1999). Motor fluctuations in Parkinson's disease. *J Neurol Sc* **165**:18-23.

29. Obeso JA, Rodriguez-Oroz MC, Chana P, Lera G, Rodriguez M, Olanow CW (2000). The evolution and origin of motor complications in Parkinson's disease. *Neurology* **55(Suppl 4)**:S13-S20; discussion S21-23.

30. Bloem BR, Beckley DJ, Van Dijk JG (1999). Are automatic postural responses in patients with PD abnormal due to their stooped posture? *Exp Brain Res* **124**: 481-8.

31. Pederson SW, Oberg B, Larsson LE *et al* (1997). Gait analysis, isokinetic muscle strength measurement in patients with Parkinson's disease. *Scan J Rehabil Med* **29**:67-74.

32. Schnieder JS, Diamond SG, Markham CH (1987). Parkinson's disease: Sensory and motor problems in arms and hands. *Neurology* **37**:951-6

33. Nallegowda M, Singh U, Handa G, Khanna M, Wadhwa S, Yadav SL, Kumar G, Behari M (2004). Role of sensory input and muscle strength in maintenance of balance, gait and posture in Parkinson's disease: a pilot study. *Am J* Phys *Med Rehabil* **83**: 898-906.

34. Escola L, Michelet T, Douillard G *et al* (2002). Disruption of the proprioceptive mapping in the medial wall of parkinsonian monkeys. *Ann Neurol* **52**:581-7.