"A CLINICAL PROFILE OF NON MOTOR SYMPTOMS IN PARKINSON'S DISEASE" – A ONE YEAR CROSS SECTIONAL STUDY

REG NO. BG0110002

Dissertation

Submitted to the
KLE University, Belgaum, Karnataka

In Partial Fulfillment
of the requirements for the degree of

M. D.

in

GENERAL MEDICINE

DEPARTMENT OF MEDICINE,
JAWAHARLAL NEHRU MEDICAL COLLEGE,
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ENDORSEMENT

This is to certify that the dissertation entitled **"A CLINICAL PROFILE OF NON MOTOR SYMPTOMS IN PARKINSON'S DISEASE" – A ONE YEAR CROSS SECTIONAL STUDY** is a bonafide research work done by **CANDIDATE REG NO. BG0110002.**

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LIST OF ABBREVIATIONS USED

APOE	-	Apo-lipoprotein E
APR	-	Age adjusted Prevalence rate
BST	-	Base Pair of somatostatin
DAT	-	dopamine transporter
DLB	-	Dementia with Lewy Bodies
EDS	-	Excessive daytime sleepiness
EXPRESS	-	The EXelon in PaRkinson's disEaSe dementia Study
H&Y	-	Hoehn and Yahr
LB	-	Lewy Bodies
LRRK	-	Leucine rich Repeat Kinase
MAPT	-	Micro Tubule Associated Protein Tau
MMSE	-	Mini Mental Status Examination
MPTP	-	Methyl Phenyl Tetrahydro Pyridine
mRNA	-	Messenger Ribo Nucleic Acid
MSA	-	Multiple System Atrophy
NMS	-	Non Motor Symptoms
NMSQuest	-	Non Motor symptoms Questionaire
OD	-	Olfactory Dysfunction
OH	-	Orthostatic Hypotension
PARK	-	Parkin
PD	-	Parkinson's Disease.
PSP	-	Progressive supranuclear palsy
QSART	-	Quantitative sudomotor axon reflex test for sudomotor function,

RBD	-	REM sleep behaviour disorder
REM	-	Rapid Eye Movement
RLS	-	Restless Leg Syndrome
SPECT	-	Single photon emission computerized tomography
SSRI	-	Selective serotonin uptake inhibitors
TCA	-	Tricyclic antidepressants
UKPDS	-	United Kingdom parkinson's Disease Society
UPDRS	-	The Unified Parkinson's Disease Rating Scale
UPS	-	Ubiquitin-proteasome system
WHO	-	World Health Organisation

ABSTRACT

Background and objectives

The nonmotor symptoms are universal features of idiopathic PD. They add significantly to the overall disability caused by PD and are the critical determinants of health related quality of life of affected patients. The present study was undertaken to assess the prevalence of prevalence of NMS in PD patients and to classify and analyse the NM symptoms on the basis of system involvement.

Methodology

The present study was undertaken to study the clinical profile of non motor symptoms in patients with PD, with the primary objective to know the prevalence of non motor symptoms in patients with PD and to classify and analyse the NMS on basis of systems involved.

Results

In the present study, prevalence of PD was more in the males compared to the females. The mean age of the study population was 57.92±9.03 and the mean duration of illness in our study was 2 years. Mean number of NMS among the study subjects was 13.2±3.55. The majority of the patients belonged to H and Y stage 3.0 and further, as the stage of the disease increased the mean number of non motor symptoms increased. Decreased libido was the most common autonomic symptom among PD patients. Among the gastro intestinal symptoms, unsatisfactory voiding of the bowel was the most common symptom accounting for 70% (n=35) Dementia, anhedonia, and attention deficits were common

neuropsychiatric symptoms with 62% (n=31) each. Sensory symptoms of olfactory disturbances and unexplained pains were present in 64% (n=32) and 82% (n=41) patients respectively.

Conclusion and interpretation

The non motor symptoms were universally prevalent in all the patients with Parkinson's disease. The number of non motors symptoms increased as the stage of the Parkinson's disease progressed. Insomnia and unexplained pains were the most prevalent non motor symptoms.

Keywords

Hoehn and Yahr Staging; Non motor symptoms; Parkinson's disease;

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Chapter 1

Introduction

INTRODUCTION

Parkinson's disease (PD) is the second most common neurodegenerative disorder, after Alzheimer's disease.[1] It is a common neurodegenerative disorder a synucleinopathy with a prevalence of 160/100,000 in Western Europe rising to 4% of the population over 80.[2] Many affected patients are older than 55 years of age, and men seem to be slightly more predominantly affected than women.[3]

Community-based series have accounted PD for more than 80% of all Parkinsonism, with a prevalence of approximately 360 per 100,000 and an incidence of 18 per 100,000 per year.[4] Among the subjects with Parkinsonism visiting the movement disorder clinics, approximately 80 to 85% have PD, the rest belonging to the categories of atypical Parkinsonism and secondary Parkinsonism.[5] Parkinson's disease afflicts approximately one million individuals in the United States (~1% of those over 55 years).[5] Another study reported that about 1% of population above the age of 65 years and about 5% above the age of 80 years suffer from PD.[6]

It can, therefore, be calculated that in India alone with an estimated population of over one billion by the turn of the century, approximately 700 million people will be above the age of 65 years, of which about 7 million will suffer from PD.[3]

PD results from degeneration of the substantia nigra pars compacta and the consequent dysfunction of the dopaminergic nigrostriatal pathway. Serotonergic and noradrenergic pathways are also affected. The pathologic hallmark is a deterioration of the substantia nigra of yet unknown causes,

resulting in a deficiency of dopamine, an important neurotransmitter for the basal ganglia circuit. A combination of genetic and environmental factors is likely to be important in producing abnormal protein aggregation within select groups of neurones, leading to cell dysfunction and then death. Understanding of the pathogenesis of the disease has been advanced in the last decade with the identification of several gene mutations which may shed light on the mechanisms of pathogenesis in sporadic cases of PD.[7]

The diagnosis of PD remains essentially a clinical one, and it is important to recognize the early features together with symptoms and signs suggesting other causes of parkinsonism. With an ageing population, the management of PD is likely to prove an increasingly important and challenging aspect of medical practice for neurologists and general physicians.[7]

The classic motor features of Parkinson disease typically start insidiously and emerge slowly over weeks or months, with tremor being the most common initial symptom. The three cardinal signs of Parkinson disease are resting tremor, rigidity, and bradykinesia. Postural instability (balance impairment) is sometimes listed as the fourth cardinal feature. However, balance impairment in Parkinson disease is a late phenomenon, and in fact, prominent balance impairment in the first few years suggests that Parkinson disease is not the correct diagnosis.[8]

When a patient presents with tremor, the clinician evaluates the patient's history and physical examination findings to differentiate Parkinson disease tremor from other types of tremor. In patients with parkinsonism, careful attention to the history is necessary to exclude causes such as drugs, toxins, or

trauma. Other common causes of tremor include essential tremor, physiologic tremor, and dystonic tremor.[8]

It has been recognized that non-dopaminergic and non-motor symptoms are sometimes present prior to diagnosis and these inevitably emerge with disease progression, impacting on morbidity, quality of life and mortality. The non-motor symptoms (NMS) of Parkinson's disease continue to be poorly recognized and inadequately treated in contrast with motor symptoms and a modern holistic approach to treatment of Parkinson's disease should therefore include recognition and assessment of non-motor symptoms.[7]

Clinical research over the last two decades has revealed that the nonmotor symptoms of Parkinson's disease involve several body systems and are a major cause of disability in these patients. They are usually under diagnosed and are difficult to treat.[7]

The nonmotor symptoms (NMSs) of Parkinson’s disease (PD) have received a lot of attention in the last few years. Despite this fact, they have still been underrecognized and undertreated.[9,10] NMS may include cognitive problems, apathy, depression, anxiety, hallucinations, and psychosis as well as sleep disorders, fatigue, autonomic dysfunction, sensory problems, and pain.[9] Since these symptoms substantially contribute to patients’ quality of life and are a frequent cause of hospitalization and institutionalization, the NMSs and their management have been recognized for Clinical Excellence as an important unmet need in PD.[11]

Most literature on the nonmotor symptoms of PD has appeared from the western countries. Though, India has a large and growing population of elderly people and PD is common among them affecting about 100 per lakh population, only few studies have documented the non motor symptoms of PD in Indian context. Hence the present study was undertaken to assess the prevalence of prevalence of NMS in PD patients and to classify and analyse the NM symptoms on the basis of system involvement.

Chapter 2

Objectives

OBJECTIVES

1. To find out the prevalence of Non Motor Symptoms in Parkinson's disease patients.

2. To classify and analyze the Non Motor Symptoms in Parkinson's disease on the basis of system involvement.

Chapter 3

Review of Literature

REVIEW OF LITERATURE

Parkinson's disease (PD), the second most common neurodegenerative disorder after Alzheimer's disease. It is a progressive neurological disorder characterised by tremor, rigidity, and slowness of movements, and is associated with progressive neuronal loss of the substantia nigra and other brain structures.[7]

Historical aspects

Parkinson's disease was first medically described as a neurological syndrome by James Parkinson in 1817, though fragments of Parkinsonism can be found in earlier descriptions. As examples, Sylvius de la Boë wrote of rest tremor, and Sauvages described festination. Much earlier, traditional Indian texts from approximately 1000 BC and ancient Chinese sources also provide descriptions that suggest Parkinson's disease. In succinct and pithy English, Parkinson captured the clinical picture: Involuntary tremulous motion, with lessened muscular power, in parts not in action and even when supported; with a propensity to bend the trunk forward, and to pass from a walking to a running pace: the senses and intellects being uninjured.[12]

Jean-Martin Charcot, in his teaching at the Salpêtrière over 50 years later, was more thorough in his descriptions and distinguished bradykinesia as a separate cardinal feature of the illness: Long before rigidity actually develops, patients have significant difficulty performing ordinary activities, this problem relates to another cause. In some of the various patients I showed you, you can easily recognize how difficult it is for them to do things even though rigidity or tremor is not the limiting feature. Instead, even a cursory exam demonstrates that

their problem relates more to slowness in execution of movement rather than to real weakness. In spite of tremor, a patient is still able to do most things, but he performs them with remarkable slowness. Between the thought and the action there is a considerable time lapse. One would think neural activity can only be effected after remarkable effort.[12]

Charcot and his students described the clinical spectrum of this disease, noting two prototypes, the tremulous and the rigid/akinetic form. They described in full detail the arthritic changes, dysautonomia, and pain that can accompany Parkinson's disease. Charcot was also the first to suggest the use of the term "Parkinson's disease" rejecting the earlier designation of paralysis agitans or shaking palsy, because he recognized that Parkinson's disease patients are not markedly weak and do not necessarily have tremor.[12]

William Gowers, working in London, contributed an important study of Parkinson's disease demographics in his "Manual of Diseases of the Nervous System," describing his personal experience with 80 patients in the 1880s. He correctly identified the slight male predominance of the disorder and studied the joint deformities typical of the disease. Known for his descriptive prose, Gowers offered one of the most memorable similes regarding Parkinsonian tremor.[12]

The movement of the fingers at the metacarpal-phalangeal joints is similar to that by which Orientals beat their small drums. Further clinical descriptions and studies of the pathologic changes related to Parkinson's disease were predominantly reported by the French neurologic school. Richer and Meige (1895) provided clinical and morphologic details of the progressive stages of

Parkinsonian disability, and the former provided drawings and statues that remain among the most important pictorial documents related to Parkinson's disease. Babinski commented on the strange motor fluctuations intrinsic to the disease itself.[12]

Brissaud first proposed damage to the substantia nigra as the anatomical seat of Parkinson's disease, and Trétiakoff and Foix and Nicolesco pursued further pathologic studies of the midbrain in relationship to the disease during the 1920s.[12]

The most complete pathologic analysis of Parkinson's disease and the clear delineation of the brain stem lesions was performed in 1953 by Greenfield and Bosanquet. The morbidity and clinical progression of Parkinson's disease was studied in the important article by Hoehn and Yahr in which their internationally recognized staging system was first introduced. This time-honored staging system is anchored in the distinction between unilateral (Stage I) disease and bilateral disease (Stages II–V) and the development of postural reflex impairment (Stage III) as a key turning point in the disease's clinical significance.[13]

Epidemiology

Incidence

The incidence of Parkinson disease has been estimated to be 4.5-21 cases per 100,000 population per year, and estimates of prevalence range from 18 to 328 cases per 100,000 population, with most studies yielding a prevalence of approximately 120 cases per 100,000 population. The wide variation in reported

global incidence and prevalence estimates may be the result of a number of factors, including the way data are collected, differences in population structures and patient survival, case ascertainment, and the methodology used to define cases.[14]

The incidence and prevalence of Parkinson disease increase with age, and the average age of onset is approximately 60 years. Onset in persons younger than 40 years is relatively uncommon. Parkinson disease is about 1.5 times more common in men than in women.[8]

Prevalence

Overall prevalence in door-to-door studies ranged from 167 to 5,703 per 100,000, with those studying an elderly population (above 60 or 65 years) reporting the highest figures.[15-17]

In studies using registries or other case-finding strategies, overall prevalence ranged between 31 and 970 per 100,000, although most studies reported prevalence between 100 and 300 per 100,000. A review based on 12 high-quality US and European studies estimated the PD prevalence among people 65 years or older at 950 per 100,000, equivalent to 349,000 affected individuals in the US.[18]

Another study that used data from six European prevalence studies and country-specific population structure data estimated the number of individuals above age 50 with PD in the world at between 4.1 and 4.6 million in 2005. By

year 2030 the number was projected to more than double to between 8.7 and 9.3 million.[19]

Several studies reported lower prevalence of PD in Africa, Asia and South America compared to Europe. To facilitate comparison among 25 studies conducted in different countries, a review[20] calculated age-standardized prevalence proportions using the US population in 1970 as the standard. They reported a 13-fold difference in age-standardized prevalences with an average prevalence of 103 per 100,000.

Regions with comparatively low estimated prevalence included Japan, China, Libya, Sardinia and Poland.[20] In contrast, a Chinese study that directly examined 29,454 individuals (94% of the study population) reported a prevalence of 1,700 per 100,000 in individuals above 65 years[17] whilst a prevalence of 3,300 per 100,000 above 65 years was found in Brazil.[21] Thus, these results were similar to European countries, questioning whether the low prevalences in China and South America resulted from differences in methodology, rather than true ethnic differences.

Age

There are no or very few cases occurring before 40 years. Also, the incidence of PD clearly increases with age steeply after age 60. However, several studies reported that incidence rates dropped in older age groups.[22] It is still a matter of debate whether this decline is real or due to underdiagnosis.

A study that included individuals with dementia as well as PD reported that incidence increased slightly with age but still dropped after 89 years.[23] Nevertheless, several studies reported increasing incidence rates up to 85 years.[24,25]

In line with incidence studies, prevalence of PD clearly increases with age. However, some studies reported a decline in prevalence in the oldest age group (above 80 or more) perhaps due to underdiagnosis of PD because of comorbidity, non-response, and unstable estimates due to small numbers in old age groups.[26]

Race

Most incidence studies were conducted in Europe, with overall incidence rates between 9 and 22 per 100,000 person-years.[24] European studies based on populations above 55 or 65 years showed relatively little variation, with overall incidence rates between 410 and 529 per 100,000 person-years.[27]

Asian studies reported overall incidence rates between 1.5 and 17 per 100,000 person years.[26] An additional study in Singapore reported an incidence rate of 32 per 100,000 person-years among individuals 50 years or above.[28] In this study, incidence among Indians was higher than that among Chinese and Malays, but numbers were small.

In general, few studies examined whether incidence differed by ethnicity although in a male North American population, incidence of PD was higher among Blacks.[29]

In a multi-ethnic population in California,[25] incidence of PD was highest among Hispanics, followed by non-Hispanic Whites, Asians and Blacks. In sum, although incidence data for PD are limited (especially for populations other than White), there are indications of ethnic differences.

Variations in PD incidence across ethnic groups might give clues about etiology, including differential environmental exposures or susceptibility genes. However, comparison among incidence studies of PD is hampered by differences in methodology and reporting. For example, some studies provided crude incidence rates, others incidence rates adjusted to different standard populations

Sex

The incidence of PD seems to be higher in men than in women. A meta-analysis of 7 door-to-door incidence studies showed a male to female ratio of 1.49 (95% confidence interval (CI) 1.24–1.95).[30]

Similarly, another meta-analysis based on 17 incidence studies of PD reported a pooled age-adjusted male to female ratio of 1.46 (95% CI 1.24–1.72) with significant heterogeneity between studies.[31]

Suggested explanations for the male preponderance include protective effects of estrogens, higher frequency of intensity of occupational toxin exposure as well as minor head trauma in men, and recessive susceptibility genes on the X chromosome.[30,31]

Several studies reported higher prevalence in men than in women,[32] although other studies found no gender difference.[33]

Mortality and morbidity

A few studies estimated cumulative incidence of PD adjusted for the competing risk of death (lifetime risk). Based on data from the Rochester Epidemiology Project, the lifetime risk was estimated at 2% in men and 1.3% in women. From age 40, the remaining lifetime risk was 1.7% overall. Men had a higher incidence, but the gender difference decreased with increasing age, as men had higher mortality rates than women.[34] A considerably higher lifetime risk was reported by the Physicians Health Study (6.7% after age 45).[23] This finding was interpreted as probably due to the longevity of the Physicians Health Study cohort. Another possible explanation is over diagnosis.

Mortality

Data from six European mortality studies showed a decreased life expectancy in all age groups, more pronounced among patients with early onset of PD.[35]

For PD patents with onset between age 40 and 64, life expectancy was 21 years versus 31 years for the general population and for PD patients with onset 65 years or above, 5 years versus 9 years.[35]

Indian perspectives

Epidemiological correlates of PD in the Indians are estimated from studies examining neurological disorders and they mainly focus on prevalence. The method to screen all disorders is similar and, possibly, there could be a bias in case identification.[36]

Bharucha et al specifically studied the prevalence of PD in the Parsi community and found rates varying between 6-328/105.[37,38] Studies from non-Parsi communities show low prevalence rates of PD, varying from 14-41/105.[37,38] PD forms 5-60% of total movement disorders with variations in geographical areas. PD was more prevalent in rural (41/105) than urban (14/105) population and was commoner among men. Age specific rates increase from 28 (in 4th decade) to 573 per 105 in ninth decade.[36]

Among hospital-based series[39] of 2,34,021 new patients, 27% had neurological disorders, of which 20% had movement disorders and PD was the third common neurological disorder and the commonest movement disorder (86.5%).

A study[40] among residents living in elderly homes (age >60 years) in Bangalore, showed that 24% had parkinsonism, with PD being the commonest (71%) followed by drug-induced parkinsonism (2.5%), multiple system atrophy (2.5%), vascular parkinsonism (1.7%), progressive supranuclear palsy (0.8%) and unclassified (22%).13 Thus, despite methodological differences across various studies and in different settings, PD is a common neurological problem in India.

Prevalence rates are influenced by case screening diagnostic methods and determinants like literacy, culture and others. All Indian epidemiological studies have estimated prevalence rates of neurological illnesses using door-to-door survey; this is preferable in a country with varying levels of education and use of medical services.[36]

They also use different types of personnel for collecting information and in different geographical settings. Population was screened using WHO protocol for neurological disorders or its variation but the sensitivity, specificity and predictive value of which vary. On the contrary, Bharucha used a standardized questionnaire to screen PD.[36]

Literacy and language pose problems in screening, therefore if another individual responds for the affected person and their understanding of PD might influence prevalence rates. Thus, it is important to develop culturally suitable screening instruments, train personnel, and include locally relevant questions for detecting PD. There has been recently modified the questionnaire developed by Tanner et al, to screen PD and have confirmed its use in India.[36]

Diagnosis of PD in population-based studies is another important issue and presence of at least two of the three cardinal features of PD resting tremor, bradykinesia, rigidity without other cause of Parkinsonism is acceptable.[36]

The BURN study had an operation manual and this and Bharucha's study used a case definition for PD. Bharucha et al[37,38] noted that Parsis have an age-adjusted prevalence rate (APR) of PD similar to white Caucasians but this figure is two times higher than other Indian studies.[40,41] The study differs from other Indian studies in terms of an urban setting and includes an ethnically different population. While causes are unclear, genetic origin of Parsis may explain the strikingly higher prevalence of PD in them.[36]

Classification of parkinsonian syndromes[43]

Etiology

Degenerative (sporadic)

- Idiopathic Parkinson's disease
- Dementia with Lewy bodies
- Progressive supranuclear palsy
- Corticobasal degeneration
- Multisystem atrophy
- Olivopontocerebellar atrophy
- Striatonigral degeneration
- Shy-Drager syndrome

Degenerative (familial)

- Early onset Parkinson’s disease.
- Huntington's disease
- Neuroacanthocytosis
- Machado-Joseph disease
- Progressive subcortical gliosis
- Familial frontotemporal dementia

Secondary Parkinsonian syndromes

- Drug-induced Parkinsonism
- Vascular Parkinsonism
- Normal-pressure hydrocephalus
- Whipple's disease
- Dementia pugilistica

Inherited metabolic disorders

- Wilson's disease
- Hallevorden-Spatz disease
- Idiopathic basal ganglia calcification[4]

Pathophysiology, aetiology and pathogenesis

The pathological hallmark of PD is cell loss within the substantia nigra particularly affecting the ventral component of the pars compacta. By the time of death, this region of the brain has lost 50–70% of its neurons compared with the same region in unaffected individuals. The earliest documented pathological changes in PD have been observed in the medulla oblongata/pontine tegmentum and olfactory bulb. In these early stages Braak stages 1 and 2 patients are pre-symptomatic. As the disease advances Braak stages 3 and 4 the substantia nigra, areas of the midbrain and basal forebrain become involved. Finally, the pathological changes appear in the neocortex.[7]

This pathological staging is based on the distribution of lewy bodies. Lewy bodies are the pathological hallmark of PD. They are a-synuclein-immunoreactive inclusions made up of a number of neurofilament proteins together with proteins responsible for proteolysis. These include ubiquitin, a heat shock protein which plays an important role in targeting other proteins for breakdown. Mutations in the a-synuclein gene are responsible for some familial forms of PD in which lewy bodies are also seen. Mutations in the parkin protein produce a parkinsonian syndrome without lewy bodies in juvenile cases suggesting that the parkin protein plays an important role in the development of the lewy body. It has been shown that parkin facilitates the binding of ubiquitin (ubiquination) to other proteins such as the a-synuclein interacting protein synphilin-1 leading to the formation of lewy bodies. Lewy bodies are found in PD and Dementia with lewy bodies (DLB), but are not a pathological hallmark of any other neurodegenerative disease.[7]

The identification of single gene defects in PD has focused interest on the ubiquitin-proteasome system (UPS) as one potential candidate in the development of cell death.5 The UPS is important for intracellular proteolysis and a large number of intracellular processes that maintain the viability of cells. It does this by removing unwanted proteins that are no longer required by the cell. Failure of the UPS leads to the abnormal aggregation of proteins including a-synuclein which are a major component of lewy bodies. One of the first sites for LB deposition in early PD is the olfactory bulb. It is, therefore, of interest that a disturbance in smell and taste is often one of the earliest clinical features in PD raising the possibility that LB formation may be integral for the activation of pathways leading to neuronal dysfunction and death. The link between UPS and neurodegeneration has been strengthened by the discovery of mutations in genes which code for several ubiquitin-proteasome pathway proteins in PD.[7]

It remains unclear why dopaminergic neuronal cell death and Lewy body formation occur in PD. The pathological changes in PD are seen not only in the SNc but also in the locus coeruleus, pedunculo pontine nucleus, raphe nucleus, dorsal motor nucleus of the vagal nerve, olfactory bulb, parasympathetic as well as sympathetic post-ganglionic neurons, Mynert nucleus, and the cerebral cortex.[44]

Widespread neuropathology in the brainstem and cortical regions are responsible for various motor and non-motor symptoms of PD. Although dopamine replacement therapy improves the functional prognosis of PD, there is currently no treatment that prevents the progression of this disease.

Genetics

The pathological mechanisms and causes of PD remain largely unknown. Most PD patients have not been associated with a particular genetic background or certain exposure of environmental toxins. However, Japanese and European groups performed genome-wide association studies and revealed that the α-synuclein locus, the MAPT locus, the LRRK2 locus, the BST1 locus, and 1q32 (PARK16) may be genetic risk factors for PD (Satake et al. 2009, Simon-Sanchez et al. 2009). Although the α-synuclein locus, LRRK2 locus, and PARK16 are confirmed as genetic risk factors for PD across populations, BST1 and MAPT may be risk loci correlated with ethnic differences. Conversely, α-synuclein is involved in the virulent effects of the environmental toxin MPTP. High mRNA and protein levels of α-synuclein have been described in the brains of MPTP-treated mice.[45]

Although α-synuclein-deficient mice exhibited marked resistance to MPTP-induced degeneration of dopamine neurons, some lines of α-synuclein transgenic mice have exhibited increased sensitivity to MPTP. These results also suggest that various genetic-environmental interactions may have influences on dopaminergic neuronal metabolism and kinetics, such as signal transduction, vesicle transport, autophagy (mitophagy), and mitochondrial stress. In addition, a prion-like transmission of α-synuclein may trigger the development of nigral degeneration in PD. Taken together, the new findings based on the interaction between familial PD-related proteins and environmental factors could shed light on the pathomechanisms for PD.

Environmental factors

Identifying environmental factors that predispose to the development of PD has proved elusive. Living in a rural environment appears to confer an increased risk of PD, and perhaps causally linked to this some but not all epidemiological studies have shown a correlation between exposure to pesticide use and wood preservatives. The only consistent environmental factor is a strong negative correlation between cigarette smoking and the development of the disease. It is also possible that mitochondrial dysfunction in PD is triggered by one or more environmental toxins.[7]

Cardinal motor clinical features

There are four cardinal features of PD that can be grouped under the acronym TRAP: *T*remor at rest, *R*igidity, *A*kinesia (or bradykinesia) and *P*ostural instability. In addition, flexed posture and freezing (motor blocks) have been included among classic features of parkinsonism, with PD as the most common form. Because of the diverse profiles and lifestyles of those affected by PD, motor and non-motor impairments should be evaluated in the context of each patient's needs and goals.[47]

A number of rating scales are used for the evaluation of motor impairment and disability in patients with PD, but most of these scales have not been fully evaluated for validity and reliability. The Hoehn and Yahr scale is commonly used to compare groups of patients and to provide gross assessment of disease progression, ranging from stage 0 (no signs of disease) to stage 5 (wheelchair bound or bedridden unless assisted). The Unified Parkinson's Disease Rating

scale (UPDRS) is the most well established scale for assessing disability and impairment. Studies making use of UPDRS to track the progression of PD suggest that the course of PD is not linear and that the rate of deterioration is variable and more rapid in the early phase of the disease and in patients with the postural instability gait difficulty (PIGD) of PD. The current UPDRS is undergoing revisions so that the revised scale will be more sensitive to detect small changes and it will integrate non-motor elements of PD. Other types of rating scales include those that assess psychiatric manifestations (depression) and quality of life. The most frequent clinical features associated with PD are listed in table and are discussed in the following sections.[47]

Parkinson's disease symptoms[47]

Motor symptoms	Non-motor symptoms
Tremor, bradykinesia, rigidity, postural instability	Cognitive impairment, bradyphrenia, tip-of-the-tongue (word finding) phenomenon
Hypomimia, dysarthria, dysphagia, sialorrhoea	Depression, apathy, anhedonia, fatigue, other behavioural and psychiatric problems
Decreased arm swing, shuffling gait, festination difficulty arising from chair, turning in bed	Sensory symptoms: anosmia, ageusia, pain (shoulder, back), paresthesias
Micrographia, cutting food, feeding, hygiene, slow activities of daily living	Dysautonomia (orthostatic hypotension, constipation, urinary and sexual dysfunction, abnormal sweating, seborrhoea), weight loss
Glabellar reflex, blepharospasm, dystonia, striatal deformity, scoliosis, camptocormia	Sleep disorders (REM behaviour disorder, vivid dreams, daytime drowsiness, sleep fragmentation, restless legs syndrome)

Bradykinesia

Bradykinesia refers to slowness of movement and is the most characteristic clinical feature of PD, although it may also be seen in other disorders, including depression. Bradykinesia is a hallmark of basal ganglia disorders, and it encompasses difficulties with planning, initiating and executing movement and with performing sequential and simultaneous tasks. The initial manifestation is often slowness in performing activities of daily living and slow movement and reaction times. This may include difficulties with tasks requiring fine motor control (buttoning, using utensils). Other manifestations of bradykinesia include loss of spontaneous movements and gesturing, drooling because of impaired swallowing, monotonic and hypophonic dysarthria, loss of facial expression (hypomimia) and decreased blinking, and reduced arm swing while walking. Given that bradykinesia is one of the most easily recognisable symptoms of PD, it may become apparent before any formal neurological examination. Assessment of bradykinesia usually includes having patients perform rapid, repetitive, alternating movements of the hand (finger taps, hand grips, hand pronation–supination) and heel taps and observing not only slowness but also decrementing amplitude.[47]

Although the pathophysiology of bradykinesia has not been well delineated, it is the cardinal PD feature that appears to correlate best with degree of dopamine deficiency. This is supported by the observation of decreased neuronal density in the substantia nigra in elderly patients with parkinsonism regardless of PD diagnosis. In addition, positron emission tomography in patients

with PD has demonstrated that the decreased F-fluorodopa uptake in the striatum and accumbens–caudate complex is proportional to the degree of bradykinesia.[47]

It is hypothesised that bradykinesia is the result of a disruption in normal motor cortex activity mediated by reduced dopaminergic function. Functional neuroimaging studies also suggest impairment in the recruitment of cortical and subcortical systems that regulate kinematic parameters of movement (velocity). Anatomically, the deficit appears to be localised in the putamen and globus pallidus, resulting in a reduction in the muscle force produced at the initiation of movement. Analysis of electromyographic recordings showed that patients with bradykinesia are unable to energise the appropriate muscles to provide enough force to initiate and maintain large fast movements. Because patients with PD have decreased electromyographic activity, they need a series of multiple agonist bursts to accomplish larger movements.[47]

Tremor

Rest tremor is the most common and easily recognised symptom of PD. Tremors are unilateral, occur at a frequency between 4 and 6 Hz, and almost always are prominent in the distal part of an extremity. Hand tremors are described as supination–pronation ("pill-rolling") tremors that spread from one hand to the other. Rest tremor in patients with PD can also involve the lips, chin, jaw and legs but, unlike essential tremor, rarely involves the neck/head or voice. Characteristically, rest tremor disappears with action and during sleep. Some patients also report an "internal" shaking that is not associated with a visible tremor. Some patients with PD have a history of postural tremor,

phenomenologically identical to essential tremor, for many years or decades before the onset of parkinsonian tremor or other PD related features. Some studies have provided a growing body of evidence that indicates that essential tremor is a risk factor for PD.[47]

In addition to rest tremor, many patients with PD also have postural tremor that is more prominent and disabling than rest tremor and may be the first manifestation of the disease. Parkinson's related postural tremor ("re-emergent tremor") is differentiated from essential tremor in that the appearance of tremor is often delayed after the patient assumes an outstretched horizontal position. The occurrence of rest tremor is variable among patients and during the course of the disease.[47]

Rigidity

Rigidity is characterised by increased resistance, usually accompanied by the "cogwheel" phenomenon, particularly when associated with an underlying tremor, present throughout the range of passive movement of a limb (flexion, extension or rotation about a joint). It may occur proximally (neck, shoulders, hips) and distally (wrists, ankles). Reinforcing manoeuvres (voluntary movements of the contralateral limb), known as the Froment's manoeuvre, usually increase rigidity and are particularly useful in detecting mild cases of rigidity. Rigidity may be associated with pain, and painful shoulder is one of the most frequent initial manifestations of PD although it is commonly misdiagnosed as arthritis, bursitis or rotator cuff injury.[47]

Postural deformities

In addition, rigidity of the neck and trunk (axial rigidity) may occur, resulting in abnormal axial postures (anterocollis, scoliosis). Postural deformities resulting in flexed neck and trunk posture and flexed elbows and knees are often associated with rigidity. However, flexed posture generally occurs late in the disease. Striatal limb deformities (striatal hand, striatal toe) may also develop in some patients. Striatal hand is characterised by ulnar deviation of the hands, flexion of the metacarpophalangeal joints and extension of the proximal and flexion of the distal interphalangeal joints; striatal foot is characterised by extension or flexion of the toes.[47]

Other skeletal abnormalities include extreme neck flexion ("dropped head" or "bent spine"), truncal flexion (camptocormia) and scoliosis. Camptocormia is characterised by extreme flexion of the thoracolumbar spine. The condition is exacerbated by walking and is relieved by sitting, lying in the supine position or by volitionally extending the trunk when the patient leans against a wall or a high walker or a table. In addition to PD, other causes of camptocormia include dystonia and extensor truncal myopathy. Another truncal deformity is the Pisa syndrome, which is characterised by a tilting of the trunk, particularly when sitting or standing.[47]

Postural instability

Postural instability due to loss of postural reflexes is generally a manifestation of the late stages of PD and usually occurs after the onset of other

clinical features. The pull test, in which the patient is quickly pulled backward or forward by the shoulders, is used to assess the degree of retropulsion or propulsion, respectively. Taking more than two steps backwards or the absence of any postural response indicates an abnormal postural response. Postural instability (along with freezing of gait) is the most common cause of falls and contributes significantly to the risk of hip fractures. The long latency to the onset of falls differentiates PD from other neurodegenerative disorders, such as progressive supranuclear palsy (PSP) and multiple systems atrophy (MSA). In one study, the average time from onset of symptoms to the first fall was 108 months in patients with PD compared with 16.8 and 42 months, respectively, in patients with PSP and MSA.[47]

Several other factors also influence the occurrence of postural instability in patients with PD. These include other parkinsonian symptoms, orthostatic hypotension, age related sensory changes and the ability to integrate visual, vestibular and proprioceptive sensory input (kinesthesia). The fear of falling can further impair balance control in patients with PD. In one study, 38% of those evaluated experienced falls, and 13% fell more than once a week. As expected, the frequency of falls correlated with the severity of disease. Treatment (dopaminergic therapy, pallidotomy, deep brain stimulation) can improve some axial signs but usually does not robustly improve postural instability, measured by platform tilt and visual tilt. Targeting other nuclei for deep brain stimulation in addition to the subthalamic nucleus and globus pallidus, such as the zona incerta and pedunculopontine nucleus, is being explored as a potential surgical treatment of gait difficulties and postural stability.[47]

Freezing

Freezing, also referred to as motor blocks, is a form of akinesia (loss of movement) and is one of the most disabling symptoms of PD. Although freezing is a characteristic feature of PD, it does not occur universally. Freezing most commonly affects the legs during walking, but the arms and eyelids can also be involved. It typically manifests as a sudden and transient (usually <10 s) inability to move. This may include hesitation when beginning to walk (start hesitation) or a sudden inability to move the feet during specific situations (turning or walking through a narrow passage, crossing busy streets, approaching a destination). Freezing is associated with substantial social and clinical consequences for patients. In particular, it is a common cause of falls.[47]

Five subtypes of freezing have been described: start hesitation, turn hesitation, hesitation in tight quarters, destination hesitation and open space hesitation. Episodes are more severe in the OFF state and are mitigated by levodopa therapy. In addition, patients often develop tricks to overcome freezing attacks. This includes marching to command, stepping over objects (a walking stick, cracks in the floor), walking to music or a beat, and shifting body weight.[47]

Risk factors for the development of freezing include the presence of rigidity, bradykinesia, postural instability and longer disease duration.[47]

Other motor abnormalities

Patients with PD may exhibit a number of secondary motor symptoms that may impact on their functioning at home, at work and while driving. Because

of a breakdown of the frontal lobe inhibitory mechanisms, some patients display a re-emergence of primitive reflexes. One study[48] that included 41 patients with PD found that the primitive glabellar reflex was present in 80.5% of patients. This symptom was a moderately sensitive (83.3%) indicator of a parkinsonian disorder but was not specific (47.5%) for PD. Patients with PD in this study also experienced an increased frequency (34.1%) of the palmomental reflex. This symptom was not sensitive (33.3%) but was more specific (90%) than the glabellar reflex. In addition, these primitive reflexes cannot differentiate among the three most common parkinsonian disorders (PD, PSP, MSA).

Similarly, the "applause sign", initially thought to be specific for PSP, is frequently present in other parkinsonian disorders, particularly corticobasal degeneration. In some cases, unintended movements accompany voluntary activity in homologous muscles on the opposite side of the body. These so-called mirror movements may be observed in early asymmetric PD.[47]

Bulbar dysfunction manifested by dysarthria, hypophonia, dysphagia and sialorrhoea, frequently observed in patients with PD, can be equally or even more disabling than the cardinal features. These symptoms are thought to be related to orofacial–laryngeal bradykinesia and rigidity. Speech disorders in patients with PD are characterised by monotonous, soft and breathy speech with variable rate and frequent word finding difficulties, referred to as "tip-of-the-tongue phenomenon." Speech therapy, such as the Lee Silverman Voice Treatment, that emphasises efforts to improve the volume and quality of the speech, may ameliorate the symptoms of dysarthria. Dysphagia is usually caused by an

inability to initiate the swallowing reflex or by a prolongation of laryngeal or oesophageal movement. Dysphagia is often subclinical, particularly in the early course of the disease. PD related drooling may result from a decrease in swallowing.[47]

A number of neuro-ophthalmological abnormalities may be seen in patients with PD. These include decreased blink rate, ocular surface irritation, altered tear film, visual hallucinations, blepharospasm and decreased convergence. The degree of abnormality in ocular pursuit and saccades as well as antisaccades is related to the degree of disease progression. Dopaminergic therapy generally improves these changes, but one study found no difference in smooth ocular pursuit between ON and OFF periods in patients with PD. Other neuro-ophthalmological abnormalities associated with PD include apraxia of eyelid opening, limitation of upward gaze and oculogyric crises.[47]

Respiratory disturbances in patients with PD can be restrictive or obstructive. These complications are associated with substantial morbidity and mortality; pneumonia is an independent predictor of mortality in nursing home patients with PD. The obstructive pattern may be related to rigidity, cervical arthrosis or restricted range of motion in the neck, and the restrictive pattern may be related to chest wall rigidity. Respiration may also be compromised by levodopa related respiratory dyskinesia in patients with PD.[47]

Diagnosis

The characteristic features of PD are bradykinesia, rigidity and rest tremor. These may not all be present. Postural instability may be a feature,

though early postural instability backwards particularly with a history of falls is more suggestive of progressive supranuclear palsy (PSP). The clinical findings are usually asymmetrical in PD. The clinical diagnosis may often appear straightforward, though it is worth noting that post-mortem studies have shown an alternative diagnosis in up to a quarter of patients with PD diagnosed by general neurologists. Of note, there is substantially less diagnostic error in patients diagnosed in expert movement disorder clinics which strengthens the argument for early referral of patients to specialists expert in movement disorders.[7]

A number of clinical criteria have been established. Table outlines an abbreviated form of the UK Parkinson's Disease Society Brain Bank clinical diagnostic criteria. There are a number of other clinical signs that are worth highlighting. A change of handwriting with micrographia is often an early feature as is reduced facial expression. A loss of arm swing on one side is also an early and useful diagnostic feature. A glabellar tap does not seem to be particularly sensitive or specific.[7]

Although the diagnosis of PD is a clinical one, there are certain situations where investigations can prove useful. Conventional brain imaging with MRI or CT is usually not required unless an alternative diagnosis is suspected such as normal pressure hydrocephalus or vascular parkinsonism.[7]

PD–UK PDS Brain Bank diagnostic criteria[7]

Step 1: Diagnosis of a parkinsonian syndrome

- Bradykinesia (slowness of initiation of voluntary movement with progressive reduction in speed and amplitude of repetitive actions) and at least one of the following:
    - Muscular rigidity,
    - 4–6 Hz rest tremor and
    - Postural instability not caused by primary visual, vestibular, cerebellar or proprioceptive dysfunction

Step 2: Exclusion criteria for PD

- History of repeated strokes with stepwise progression of parkinsonian features
- History of repeated head injury
- History of definite encephalitis
- Oculogyric crises
- Neuroleptic treatment at the onset of symptoms
- More than one affected relative
- Sustained remission
- Strictly unilateral features after 3 years
- Supranuclear gaze palsy
- Cerebellar signs
- Early severe autonomic involvement
- Early severe dementia with disturbances of memory, language and praxis
- Babinski's sign
- Presence of cerebral tumour or communicating hydrocephalus on CT scan
- Negative response to large doses of levodopa (if malabsorption excluded)

Step 3: Supportive criteria for PD (three or more required for diagnosis of definite PD)

- Unilateral onset
- Rest tremor present
- Progressive disorder
- Persistent asymmetry affecting side of onset most
- Excellent response (70–100%) to levodopa
- Severe levodopa-induced chorea
- Levodopa response for 5 years or more
- Clinical course of 10 years or more

Single photon emission computerized tomography (SPECT) imaging using a dopamine transporter (DAT) can be helpful in differentiating PD from a number of conditions, including essential tremor and dystonic tremor, neuroleptic-induced parkinsonism and psychogenic parkinsonism all of which demonstrate normal DAT scans. Uptake within the basal ganglia is reduced in PD, the parkinsonian syndromes and DLB.[7]

NON MOTOR SYMPTOMS IN PARKINSON'S DISEASE

Parkinson's disease has traditionally been viewed as a disease with only motor features. Nowadays, a wide variety of non-motor symptoms and signs are also recognised as being characteristic of the disease. Non-motor symptoms, most importantly autonomic dysfunction, neuropsychiatric symptoms and sleep problems, are prevalent in virtually all Parkinson's disease patients and influence the quality of life more than the motor symptoms. Patients may visit a variety of health care professionals, but non-motor symptoms are often missed, because physicians do not explicitly ask patients about them or do not recognise them as being part of the disease. Knowledge of non-motor symptoms is important to avoid unnecessary additional testing. Specific treatment options are available, as described in the Dutch multidisciplinary guidelines on Parkinson's disease.[50]

Most patients of idiopathic PD present with one or more of the cardinal motor features. Apart from these, various nonmotor symptoms also occur in PD and constitute a major clinical challenge, as they are common, but often overshadowed by the dominance of motor symptoms.

The nonmotor symptoms (NMS) of PD were also recognised by James Parkinson, who referred to sleep disturbance, constipation, dysarthria, dysphonia, dysphagia, sialorrhoea, and urinary incontinence in his 'Essay on the shaking palsy' in 1817. Since then, numerous studies have indicated that nonmotor symptoms are frequent accompaniments of PD, and can significantly impair quality of life, and may precipitate hospitalisation.[50]

The nonmotor symptom complex of Parkinson's disease

Nonmotor symptoms of Parkinson's disease

- **Neuropsychiatric symptoms** Depression, apathy, anhedonia, anxiety, panic attacks, attention deficit Hallucinations, illusion, delusions, obsessional behaviour, Dementia, confusion, delirium.

- **Sleep disorders -** Restless legs and periodic limb movements, REM sleep behaviour disorder (RBD) Insomnia, excessive daytime somnolence Vivid dreaming, sleep disordered breathing.

- **Autonomic symptoms -** Bladder disturbances: urgency, nocturia, frequency Sexual dysfunction: hypersexuality, erectile dysfunction, Abnormalities of sweating, orthostatic hypotension, dry eyes, (xerophthalmia), dry mouth.

- **Gastrointestinal symptoms -** Dribbling of saliva (sialorrhoea), Delayed gastric emptying, ageusia, dysphagia, choking, reflux, Vomiting , nausea , Constipation , unsatisfactory voiding of bowel, faecal incontinence.

- **Sensory symptoms -** Pain , paraesthesia, olfactory disturbance (hyposmia).

- **Other symptoms -** Fatigue, diplopia, blurred vision, seborrhea, Weight loss; weight gain.

Because of the varieties of symptoms, the prevalence of non-motor symptoms in PD patients is difficult to delineate precisely. It is estimated that about 16–70% of patients suffer from neuropsychiatric problems, including depression, anxiety, apathy or psychosis. Cognitive deficits affect at least 20–40% of PD patients. Sleep disturbances occur in more than a third of PD patients. Dysautonomia, including constipation, orthostatic hypotension, urinary and sexual dysfunctions, is reported in more than half of the PD patients, according to a questionnaire-based study. This European study and other studies also suggest that autonomic failures, including orthostatic dizziness, bladder dysfunctions, erectile dysfunctions and hyperhidrosis, are more prevalent in PD patients than control individuals.[50]

The prevalence of nonmotor symptoms (NMS) of PD as a whole is inadequately documented because there are insufficient adequately powered, community-based studies on prevalence, effect, and treatment efficacy in relation to the nonmotor symptoms, and there is a need for large and well-designed prospective studies.[50]

Despite their impact on quality of life, the NMS of PD are not well recognised in clinical practice. One of the studies reported that existing depression, anxiety and fatigue are not identified by neurologists in over 50% of

consultations, and sleep disturbance in over 40%. Another study attempted to correlate nonmotor symptoms in PD at presentation retrospectively after clinico-pathological confirmation of diagnosis[16]. 21% had NMS at presentation and these included pain, anxiety, urinary dysfunction and depression. Some of these patients were more likely to be misdiagnosed initially and had inappropriate medical interventions. It is a common misconception that NMS occur only in late or advanced PD. NMS can present at any stage of PD including the early and pre-motor phase. Other studies suggest that several NMS of PD such as olfactory problems, constipation, depression and erectile dysfunction may antedate the motor signs, symptoms and diagnosis of PD by a number of years. It has been suggested that some NMS such as olfactory dysfunction in combination with others like rapid eye movement behavior disorder (RBD) or constipation may be useful to identify a population "at risk of PD", which will be particularly important if and when neuroprotective therapies become available.[50]

The nonmotor symptoms suggested as pre-clinical (motor) feature in PD[51]

- Constipation
- Olfactory deficit (discrimination)
- REM sleep behaviour disorder
- Depression
- Possible links
    - Restless legs syndrome
    - Apathy
    - Fatigue

- Anxiety
- Pain
- Male erectile dysfunction

A study[52] reported that NMS were present even in patients within 5 years of (motor) disease onset, and these were identified frequently with the use of a patient-completed questionnaire.

Recent studies[53] using the nonmotor questionnaire for PD (NMSQuest) have also highlighted the significant occurrence of 30 different NMS in PD in comparison to an age-matched control group (Annexure). Irrespective of the disease stage, upto 9-12 different NMS may be unmasked in most PD patients by the use of the NMSQuest at clinic visit.

The recently published PDLIFE study[53] highlighted the issue that a decision to delay treatment for PD is usually based on assessment of motor state alone, while the major deterioration may be in several nonmotor domains of PD. Therefore, in the present era, attention is being focussed on the recognition and quantification of nonmotorsymptoms, which will form the basis of improved treatments.

Pathophysiology of the Nonmotor Symptom Complex in Parkinson's Disease

The neuroanatomical and neurochemical substrates for much of the nonmotor symptom complex in PD are largely unknown.[54] The non-dopaminergic-cell dysfunction is thought to play a major part in the development of nonmotor symptom complex.[55]

The traditional view that the pathological process in PD starts with the degeneration of dopaminergic neurons in the substantia nigra has been challenged by which introduced the concept of a six-stage pathological process, beginning at clearly designated induction sites.[56,57]

In *Braak stage 1* there is degeneration of olfactory bulb and anterior olfactory nucleus which may explain olfactory dysfunction as a pre-motor NMS. *Braak stage 2* reflects progression of the pathology to lower brainstem which involves areas mediating sleep homeostasis and other autonomic features.

Sleep may be affected by abnormalities in the sleep-wake cycle – related pathway mediating thalamocortical arousal while the pedunculopontine nucleus, locus coeruleus, and serotonergic raphe nuclei are thought to be key areas related to the origin of visual hallucinations and RBD.[50] Medullary nuclei also play an important part in central autonomic control while involvement of the dorsal vagal nucleus may explain constipation in PD. The typical motor triad of tremor, rigidity, and bradykinesia only emerge at *Braak stages 3 and 4* when the stepwise neurodegenerative process has affected the substantia nigra and other deep nuclei of midbrain and forebrain. At this stage, PD crosses the threshold from a premotor disorder to a motor disorder and is clinically diagnosed. The final stages, *Braak stages 5 and 6*, correlate with the presence of Lewy bodies in limbic structures and neocortex. Patients may have neuropsychiatric symptoms such as depression, cognitive impairment, and visual hallucinations.[50]

Besides the central nervous system involvement, pathology also extends into the peripheral autonomic nervous system, involving the sympathetic ganglia,

cardiac sympathetic efferents, and myenteric plexus of the gut. Nonmotor symptoms may also occur as side effects of drugs used to treat motor symptoms. These may include orthostatic hypotension, hallucinations, somnolence, insomnia, or leg edema, adding to the overall burden of the nonmotor spectrum of parkinsonian morbidity.[50]

The Spectrum of Non-Motor Symptoms in Parkinson's Disease

Sleep Disturbances

Sleep disorders are among the most frequent nonmotor problems of PD.[58] They include difficulties falling asleep, frequent awakenings, nocturnal cramping, painful dystonia, or nocturnal motor symptoms with difficulties turning in bed, restless legs syndrome (RLS), night-time incontinence, nocturnal hallucinosis, and daytime sleepiness.[59]

REM sleep behaviour disorder (RBD)

RBD is a parasomnia characterised by loss of normal skeletal muscle atonia during REM sleep, thus enabling patients to physically enact often vivid and unpleasant dreams. RBD occurs in about a third of patients with PD and may precede the development of motor symptoms in over 40% of patients. Vocalisations (talking, shouting, vocal threats) and abnormal movements (arm or leg jerks, falling out of bed, violent assaults) are commonly reported by bed partners. Imaging studies in patients with isolated RBD, have indicated a small but significant symmetrical reduction in striatal dopaminergic uptake, which may be suggestive of preclinical PD. The pathological basis of RBD is unknown. It is

suggested that that RBD may arise due to the degeneration of lower brainstem nuclei including the pedunculopontine and subcoeruleal nucleus areas affected in Braak stages 1 and 2.[50]

Excessive daytime sleepiness

Excessive daytime sleepiness (EDS) and involuntary dozing affects up to 50% of PD patients and may also be preclinical marker for PD. Neuronal degeneration in suprachiasmatic nucleus that regulates the internal diurnal rhythm may be implicated, while hypocretin (orexin), a hypothalamic peptide may also have a regulatory role. The involvement of these areas in Braak stages 1 and 2 may explain the early occurrence of EDS. A combination of the disease process, the effect of nocturna sleep disruption, and antiparkinsonian drugs (dopamine agonists and levodopa) is probably causative.[50]

Restless legs syndrome (RLS)

RLS symptoms are often reported in PD, but prevalence studies of RLS in PD are few with inconsistent results. Underlying pathophysiology potentially shared by RLS and PD is mainly suggested by the similarities in treatment response. Some authors have reported subtle deficits in nigrostriatal terminal function based on the functional imaging studies in RLS. Further long-term studies will clarify whether or not RLS is associated with an increased risk for development of PD.[60]

Neuropsychiatric symptoms

Psychiatric syndromes as well as cognitive impairment frequently complicate PD. Development of psychopathology in PD is attributed to a number of factors, including underlying disease processes related to PD, medication effects, and psychological reactions to the illness. Up to 90% patients experience psychiatric complications, including major mood disorders (major depression, dysthymia, or bipolar disorder), adjustment disorders, anxiety syndromes, drug-induced mood changes, pathological tearfulness, dementia, apathetic states, psychosis, or delirium.[61]

Depression

The prevalence of major depression in PD is estimated to be 40%, with reported prevalence rates ranging from 4% to 70%. Major depression accounts for about half of the cases with significant depression, whereas others experience adjustment disorders, dysthymia, or bipolar disorder. The major depressive syndrome is frequently accompanied by anxiety symptoms. The diagnosis of depression in PD can be difficult because of the overlap between depressive features and the symptoms of PD itself. Accordingly, PD can be misdiagnosed as a primary depressive illness, and concomitant depression may go unrecognized in the PD patient. Even when both conditions (PD and depression) are diagnosed concurrently, it can be difficult to tease apart which clinical phenomena are related to primary motor vs. primary psychiatric pathology. A central issue is whether the major depressive syndrome in PD is a reaction to the motor disability or whether the syndrome is intrinsic to the disease processes of PD. Research

examining the theory that depression is integral to disease process has evaluated the impact of disease severity, disease duration, age of onset, and gender on depression, with no consistent relationship found between these variables and depression. The evidence that depression can precede the development of motor symptoms also suggests that depression in itself is a neurological symptom of PD. Other studies suggest that depression is a reaction to the disability, on the basis of correlations between depression severity and motor impairment. Clearly, the relationship between mood and motor phenomena in PD is complex. Further research examining the factors associated with depression in PD, especially how it relates to disability and functional status, is needed.[50]

Anxiety

Anxiety is a common problem in PD, but has gained relatively little attention. While anxiety can present as an isolated symptom or as a feature of depression, clinically significant anxiety syndromes occur in up to 40% of PD patients. Particularly common are generalized anxiety disorder, social phobia, and panic disorder, which have a prevalence rate of 25% in some series. These syndromes may also precede or accompany a major depressive syndrome, and should be regarded as distinct from anxiety, which is an understandable psychological response to motor impairment or other personal concerns.[50]

Symptoms of autonomic dysfunction can also be associated with anxiety or depression. Accordingly, somatic complaints related to autonomic symptoms (flushing, dizziness, urinary frequency, or changes in heart rate) must be evaluated carefully because they can be misdiagnosed (and mistreated), as if they

represented affective syndromes. The anxiety syndromes in PD appear related to underlying brain disease, with evidence implicating noradrenergic dysfunction. Several studies have reported that anxiety syndromes may even precede the onset of motor symptoms of PD.[50]

Psychosis

Hallucinations and delusions occur in up to 40% of PD patients and are a major precipitant of nursing home placement. Psychosis is related to dopaminergic medications in about 20% of PD patients, a relationship that tends to overshadow other important causes of psychosis in PD. Psychosis can also develop spontaneously or in association with cognitive impairment, on-off fluctuations, mood disturbance, other psychoactive medications, and/or delirium.

The psychotic syndromes are frequently categorized into three general groups:

The first group consists of visual hallucinations (vivid depictions of animals or people) occurring in a clear sensorium and accompanied by insight. *The second type* generally involves more persistent hallucinations or delusions in a clear sensorium but with diminished insight. This state often requires definitive antipsychotic treatment. In *the third group,* hallucinations or delusions occur in the context of a delirium. A population based study of psychosis showed associations among psychotic symptoms and age, stage, and diagnostic subgroup of PD, severity of depression, and cognitive impairment, whereas antiparkinsonian medications did not discriminate between the PD patients with and without psychosis. This finding suggests more widespread pathologic brain

involvement in the setting of psychosis and argues against a prominent role for antiparkinsonian medicines in the development of psychosis.[50]

Cognitive impairment

Dementia occurs in up to 40% of people with PD, a rate about six-times higher than that in healthy individuals. It is clinically characterised by a dysexecutive syndrome with impairment of visuospatial abilities and memory on a background of loss of response to dopaminergic drugs including levodopa. Degeneration of nigral cells is implicated, and although presence of cortical and subcortical Lewy bodies is also likely to be causative, this is controversial. Cholinergic cell loss in the nucleus basalis of Meynert is prominent in PD and forms the basis of cholinergic treatment for dementia in the disease. The contribution of comorbid Alzheimer's disease and vascular pathology, as well as a possible genetic association with the APOE genotype, have also been implicated. About 25% of patients develop an Alzheimer-type dementia with cortical features of aphasia, apraxia, and memory deficits. While depressive disorders can coexist with dementia in PD, families and clinicians may also misinterpret a tendency to reduce social interactions in early dementia as a sign of depression rather than impaired cognition only and seek antidepressant treatment. The distinction is important, since PD patients with dementia are especially vulnerable to psychoactive medication effects and the development of delirium, a leading cause of nursing home placement in PD.[50]

Dysautonomia

Autonomic dysfunction is an almost universal feature of PD and includes orthostatic hypotension (OH), constipation, urinary and sexual dysfunction. The pathophysiology is complex and includes degeneration and dysfunction of the nuclei mediating autonomic functions such as dorsal vagal nucleus, nucleus ambiguus, and other medullary centres, which exert differential control on the sympathetic preganglionic neurons via descending pathways. Additionally, degeneration of cholinergic, monoaminergic, and serotoninergic nuclei cause abnormalities within the central autonomic network.[50]

A study[62] of 141 patients with PD and 50 healthy age-matched controls showed that the prevalence of orthostatic dizziness, constipation, bladder dysfunction, erectile dysfunction, and hyperhidrosis was significantly higher than in controls and 50% of patients with PD rated their effect on daily living as “a lot” or “very much.”

A recent study reported that autonomic symptoms were significantly more common across all stages of PD. Significant peripheral sympathetic failure is rare in PD and clinically leads to orthostatic hypotension, which usually develops late in the disease, unlike in multiple system atrophy where it is an early manifestation.[64]

Orthostatic hypotension

One of the retrospective reviews[65] of 135 cases of pathologically proven PD reported evidence for symptomatic orthostatic hypotension (OH) in 30%, bladder dysfunction in 32%, and constipation in 36%.

In another study,[66] the tilt-table testing detected OH in 58% patients. In 20%, OH was symptomatic and correlated with dopaminergic medication dose and duration and severity of PD. Peripheral sympathetic cardiovascular denervation has been implicated as the mechanism of OH in PD, as shown in various studies.[50]

Constipation

Constipation is one of the commonest nonmotor symptoms in PD.70 Several case control studies have reported increased prevalence of constipation in PD of between 28% and 61% compared to control cases (6%-33%).[67]

One study[68] reported either constipation or prolonged intestinal transit time in as many as 80% of patients with PD. Constipation has been reported as a prominent complaint prior to the onset of motor symptom of PD in about 50% of patients in one series.[67] Lewy body pathology in the peripheral autonomic nervous system involving the myenteric plexus with subsequent colonic sympathetic denervation contributes to constipation in PD.[50]

Sexual dysfunction

Sexual dysfunction in PD may manifest as both reduced and abnormally increased sex drive. Erectile and ejaculation failure may occur. Testosterone deficiency has been implicated.[50]

A study[70] noted that 17 of 21 male patients with PD had substantial impairment of sexual arousal, behaviour, drive, and orgasm domains, whereas in those with longer duration of the disease sexual fantasy was increased.

Another study[71] reported high prevalence (76.5%) of sexual dysfunction in patients after bilateral subthalamic nucleus stimulation.80 Aberrant sexual behaviour may also occur as a part of dopamine dysregulation syndrome, due to dopaminergic drug treatment in susceptible patients.

Urinary dysfunction

This may include urinary frequency and urgency, incomplete bladder emptying, double micturition, and urge incontinence. The most common abnormality is related to detrusor hyperreflexia, while detrusor hypoactivity seems to be less prominent. Paradoxical co-contractions of urethral sphincter muscle has also been described. Urological examination and urodynamic investigations are mandatory to correctly identify the type of dysfunction underlying the patient's bladder problem and initiate appropriate treatment.[50]

Autonomic function in PD can be objectively assessed by several validated tests, including QSART (quantitative sudomotor axon reflex test for sudomotor function), urodynamic studies such as uroflowmetry and cystometry

for bladder dysfunction, defecating proctography (bowel dysfunction), 60 degrees head-up tilt test with cardiovascular monitoring (postural hypotension), sympathetic skin response, and pupil function tests with pilocarpine or phenylephrine. In cases where distinction from multiple system atrophy or other causes of primary dysautonomia is needed, tests such as urethral sphincter electromyography, catecholamine concentrations (plasma norepinephrine concentrations) in response to head-up tilting, and clonidine-induced growth hormone challenge tests could be useful.[50]

Recognition of Nonmotor Symptoms

The nonmotor symptoms of PD are frequently overlooked. In a prospective study[72] of 101 patients, the physician did not discuss important symptoms such as depression, anxiety, fatigue, and sleep disturbance with more than 50% of their patients. This finding was attributed to the possibilities such as limited consultation time, perception of the patient and the carer that their symptoms are unrelated to the disease (visual hallucinations or diplopia), non-awareness of the physician who may target only motor symptoms of PD and an expectation that non-motor symptoms will be managed in the community, usually by the family doctor or community health nurse.

However, even though the physician might not always actively treat the nonmotor symptoms, he or she might be best qualified to identify them, especially as they can often be difficult to diagnose. For example, depression may be missed (or overdiagnosed) in a patient with bradyphrenia and mask-like face, and experience is required to differentiate drug-induced and degenerative

psychosis. The identification of nonmotor symptoms can be improved by the application of quantitative and validated instruments for their assessment; for e.g., Epworth sleepiness scale (for sleep disorders), Hospital anxiety and depression scale, Hamilton depression rating scale, Beck depression inventory etc., for mood disorders, PD quality of life questionnaire, Parkinson's disease NMS questionnaire (NMSQuest), revised unified Parkinson's disease rating scale (UPDRS) etc.[73]

Sensory Symptoms and pain

Sensory symptoms in PD have been described as numbness, tingling, burning, aching, coldness, heat, and pain. James Parkinson himself noted "rheumatic pain" ipsilateral to the extremity first affected by rest tremor, and Charcot noted it in his lectures on cramps, muscular aching, rheumatoid and neuralgic pains experienced by patients with PD.[50]

Other series[74] have reported such primary sensory symptoms in 40% - 50% of patients. Pain may be related to motor fluctuations, early morning dystonia, or secondary causes such as musculoskeletal pain.[50]

Several authors[75] have noted painful sensations as the presenting symptom of PD. Spontaneous limb pain in PD is often reported as proximal and more prominent in the limb first and more severely affected.[50]

The pathophysiology underlying sensory symptoms and pain in PD is poorly understood. There is evidence that pain is probably a result of altered central pain processing as part of the neurodegenerative process. Possible

explanations include loss of dopaminergic, pain-inhibiting descending input to dorsal horn synapses due to substantia nigra or ventral tegmental dopaminergic cell loss. Dopaminergic denervation could also potentially induce central hypersensitivity to pain stimuli via basal ganglia-thalamic connections. Non-dopaminergic mechanisms could also be involved – loss of noradrenergic descending pain inhibitory input from locus ceruleus to dorsal horn of spinal cord.[76]

It has also been reported that the widespread cortical Lewy body degeneration also can afect areas of central pain processing system, including the cingulate gyrus, insular cortex, amygdala, and hypothalamus.[77]

Olfaction

Olfactory dysfunction (OD) may affect up to 90% of PD patients. In 1975, Ansari and Johnson suggested the association between olfactory dysfunction and development of PD and subsequently several other workers have established OD as a preclinical marker for PD.[50]

Studies[78] have also reported olfactory deficits in asymptomatic relatives of patients with PD, some of whom subsequently became symptomatic.

A longitudinal study[79] of 2,263 elderly men by Ross and colleagues assessed olfaction using 12 odour smell identification test and reported an association between impaired olfaction and incident PD.

These studies[78,79] lend support to the pathoanatomical association between Braak stage 1, consisting of early degeneration of extranigral neurons in the

olfactory bulb and anterior olfactory nucleus, and resultant olfactory disturbance as a preclinical or motor symptom. They also underscore the potential of olfactory function testing as a screening tool for persons at risk for PD.

Management of Non-Motor Symptoms

Robust controlled studies are virtually nonexistent for the treatment of NMS in PD. However, there is some evidence from a handful of controlled trials for the treatment of certain NMS in PD, in particular depression, cognitive decline, psychosis and EDS. Moreover, the effect of these treatments on quality of life in PD is lacking, and many trials include only small numbers of patients.

Dopaminergic treatment has some effect on depressive symptoms. Only pramipexole has been investigated for its potential beneficial effect in depression and Corrigan and colleagues reported antidepressant activity similar to fluoxetine.[80] Other dopaminergic agonists including ropinorole (not pergolide) may have the same effect. However, some studies have reported precipitation of mania with pramipexole and ropinirole.[81] Tricyclic antidepressants (TCA) and selective serotonin uptake inhibitors (SSRIs) have remained the major classes of drugs used for treatment of depression in PD. However, SSRIs such as fluoxetine or fluvoxamine should be avoided in patients receiving selegiline as it can induce the potentially fatal serotonin syndrome.

Treatment of psychosis in PD remains complicated as withdrawing dopaminergic treatment or introducing antipsychotics may worsen the parkinsonian state. However, there is good evidence that newer atypical antipsychotics, e.g., clozapine, may be beneficial.[82] The evidence of efficacy of

quetiapine is controversial as a recent trial has shown no beneficial effect of quetiapine for PD psychosis.[83] The newer antipsychotics bind loosely and dissociate rapidly from D2 receptors, allowing an almost normal dopaminergic transmission. Several studies have shown that clozapine improves the psychosis rating scales.[82] Dopaminergic treatment has a limited effect on cognitive impairment in PD. Loss of cholinergic cells forms the basis of treatment for dementia in PD. The Exelon in Parkinson's disease dementia Study (EXPRESS) for efficacy of rivastigmine in dementia associated with PD represents advances in treatment of aspects of NMS in PD using non-dopaminergic treatment.[83] The cholinesterase inhibitor rivastigmine was shown to have a significant effect on dementia in PD as rated by dementia scores.[83] In another double blind, placebo controlled trial donepezil was also shown to improve dementia.[84]

There is evidence from two small trials to support the use of modafinil for EDS in PD. Although the sample size was small, Adler and colleagues demonstrated that modafanil was effective for the treatment of EDS.[85] However, a recent larger double-blind, placebo-controlled trial in 40 patients did not show efficacy of modafinil for EDS in PD.[87] There are no controlled trials for treatment of RBD but there are claims that night-time dosing with levodopa and use of clonazepam or pramipexole may reduce involuntary nocturnal movements during sleep. Most clinical experience is based on use of clonazepam but it is necessary to exercise caution as sleep-disordered breathing may coexist with RBD and can be worsened by clonazepam.

Controlled trial evidence regarding the treatment of autonomic dysfunction in PD is only available for drooling and erectile dysfunction. Both

botulinum toxin A and B injected into the parotid and/or submandibular glands can be an effective treatment for drooling in PD.[88] Erectile dysfunction can be treated effectively in PD with the use of sildefinil without the occurrence of side effects, in particular postural blood pressure. There is little research available for treatment of constipation, which is a very common presenting symptom in PD; however, in one study, macrogol was shown to be effective.[89]

Although deep-brain stimulation of the subthalamic nucleus is an effective treatment for motor symptoms of PD, its effect on non-motor symptoms is unclear. Kalteis and colleagues reported an improvement in psychiatric symptoms such as depression, anxiety and psychological symptoms in a study of 33 patients after subthalamic nucleus deep brain stimulation.[90] There have been reports of decreased verbal and executive functioning after subthalamic nucleus deep brain stimulation.[91] Dopaminergic therapy appears to be unhelpful for most of the NMS of PD unless these are linked to motor fluctuations. Many NMS of PD may have a non dopaminergic basis and symptoms usually do not respond to dopaminergic treatment. Indeed, dopaminergic therapy may precipitate some non- motor problems in PD such as the dopamine dysregulation syndrome and orthostatic hypotension.

Chapter 4

Methodology

METHODOLOGY

The present study was conducted in the Department of Medicine, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum during the period of January 2011 to December 2011.

Study design

The study design was one year cross sectional study.

Study period and duration

The present one year study was conducted during the period of January 2011 to December 2011.

Method of collection of data

Source of Data

Patients proved to have Parkinson disease by UKPDS criteria attending Department of Medicine at KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum were studied.

Sample size

A total of 50 patients with Parkinson's disease were selected for the study.

Sampling procedure

Based on the average 80% of the past three years hospital statistics the sample size was calculated to be 50 patients.

Selection criteria

Inclusion Criteria

- Patients proved to have Parkinson's disease by UKPDS Brain Bank Criteria.

Exclusion Criteria

- History of multiple strokes.
- Patients with diabetes mellitus more than five years.
- Patients with known thyroid disorders.

Ethical clearance

The study was approved by the Ethical and Research Committee, Jawaharlal Nehru Medical College, Belgaum.

Informed Consent

All the patients fulfilling selection criteria were explained about the purpose of study and a written informed consent was obtained to participate in the study before enrollment (Annexure I).

Method of collection of data

Before the enrollment, demographic data such as age, sex and education were recorded. Patients were asked for the history regarding other neurological illness, duration and medications. Further thorough clinical examination was conducted.

The diagnosis of Parkinson's disease was confirmed by UKPDS Brain Bank Criteria. Neurological examination was conducted for MMSE scores and H and Y staging. These findings were recorded on a predesigned and pretested proforma (Annexure II).

Procedure

After the clinical evaluation, the patients were provided with NMS Questionnaire to assess of non motor symptoms. The participating patients were explained questions before completion of questionnaire.

Statistical analysis

The data obtained was coded and entered into Microsoft Excel Worksheet. The categorical data was expressed as rates, ratios and proportions and continuous variables were expressed as mean ± standard deviation.

Chapter 5

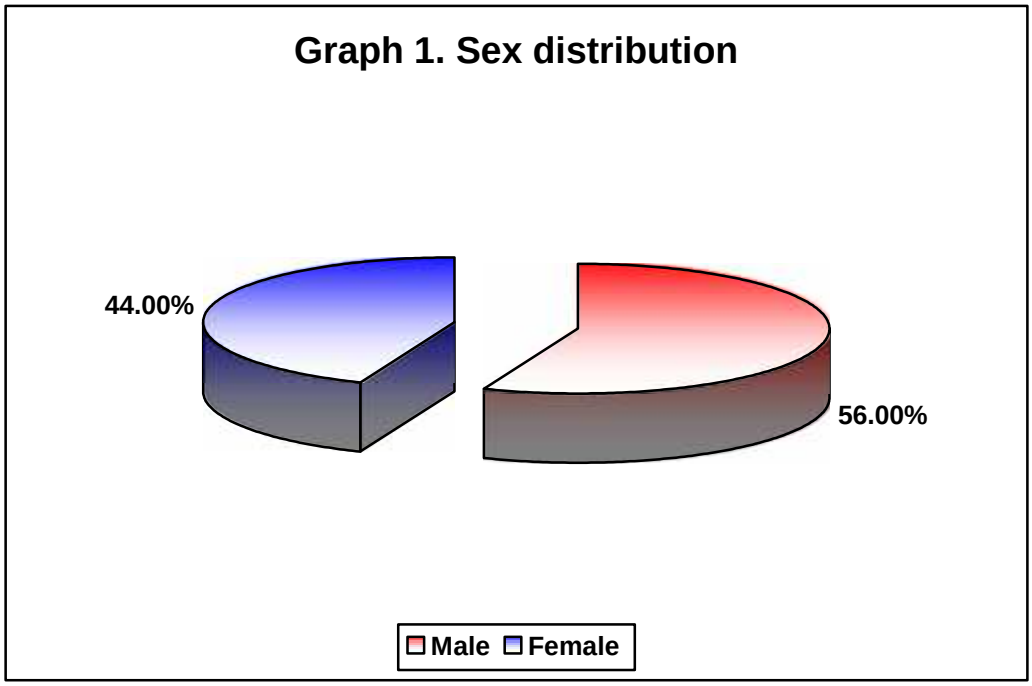
Results

RESULTS

The present one year cross sectional study was conducted in the Department of Medicine, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum during the period of January 2011 to December 2011. A total of 50 patients with Parkinson's disease proved to have Parkinson's disease by UKPDS criteria were included in the study. The data obtained was coded and entered into Microsoft Excel Worksheet. Analysis was done and the results were tabulated as below.

Table 1. Sex distribution

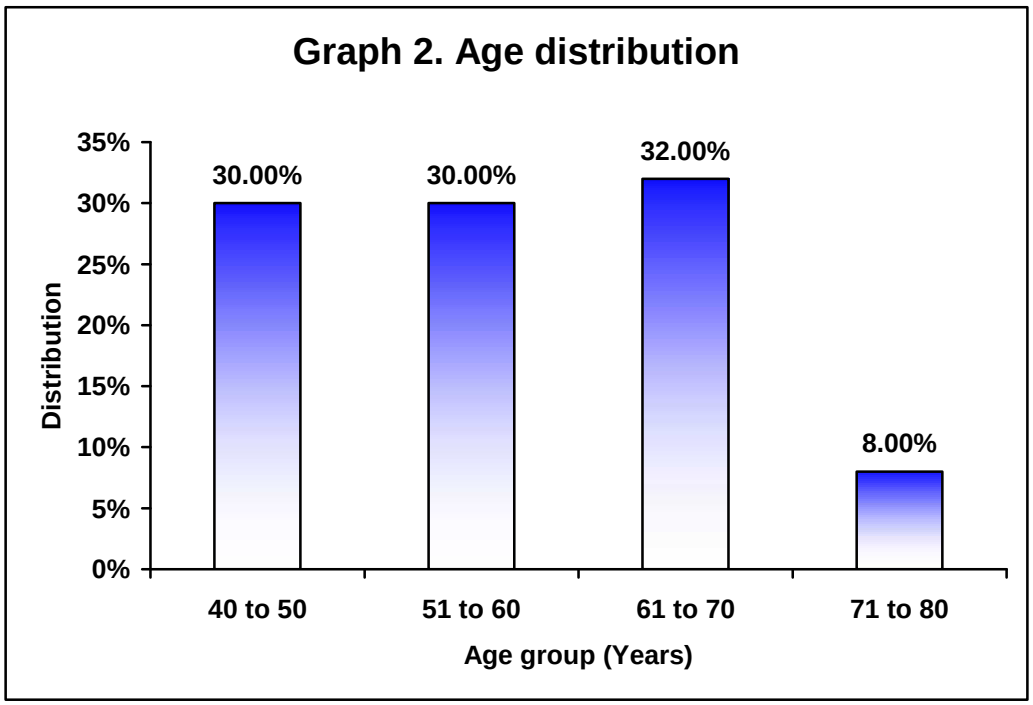
Sex	Distribution (n=50)	
	Number	**Percent**
Male	28	56.00
Female	22	44.00
Total	**50**	**100.00**



In our study of the 50 patients studied, 56% (n=28) were males and 44% (n=22) were females.

Table 2. Age distribution

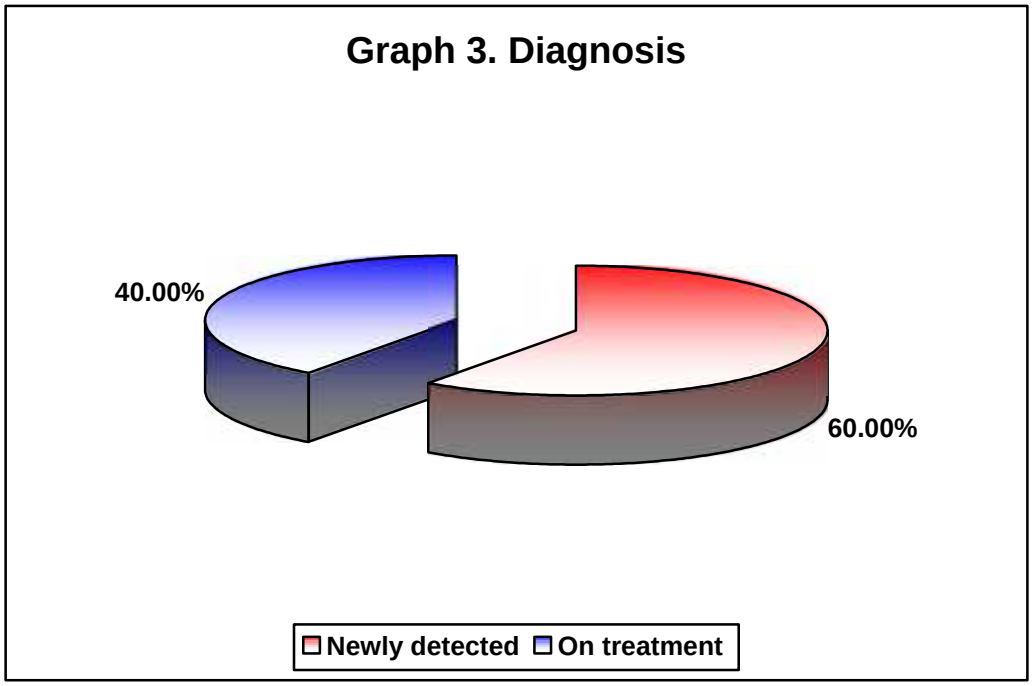
Age (Years)	Distribution (n=50)	
	Number	**Percent**
40 to 50	15	30.00
51 to 60	15	30.00
61 to 70	16	32.00
71 to 80	4	8.00
Total	**50**	**100.00**



In our study, it was observed that highest number of patients (32%) belonged to the age group of 61-70 years. The next highest number of patients belonged to the age group of 40-50 years (30%) and 51-60 years(30%) . Only 8% of the patients were aged above 70 years. The mean age was 57.92±9.03.

Table 3. Diagnosis

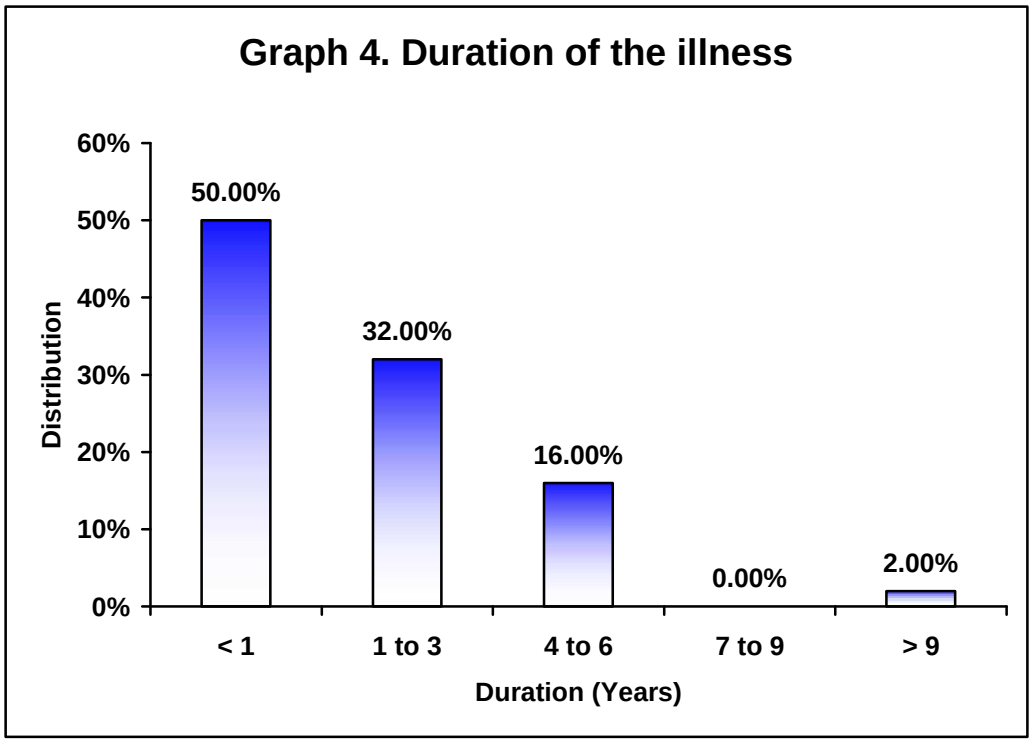
Diagnosis	Distribution (n=50)	
	Number	**Percent**
Newly detected	30	60.00
On Treatment	20	40.00
Total	**50**	**100.00**



In our study of the total 50 patients, 60 % (n=30) were newly diagnosed patients of Parkinson's disease. The remaining 40% (n=20) were known patients of Parkinson's disease on treatment.

Table 4. Duration of the illness

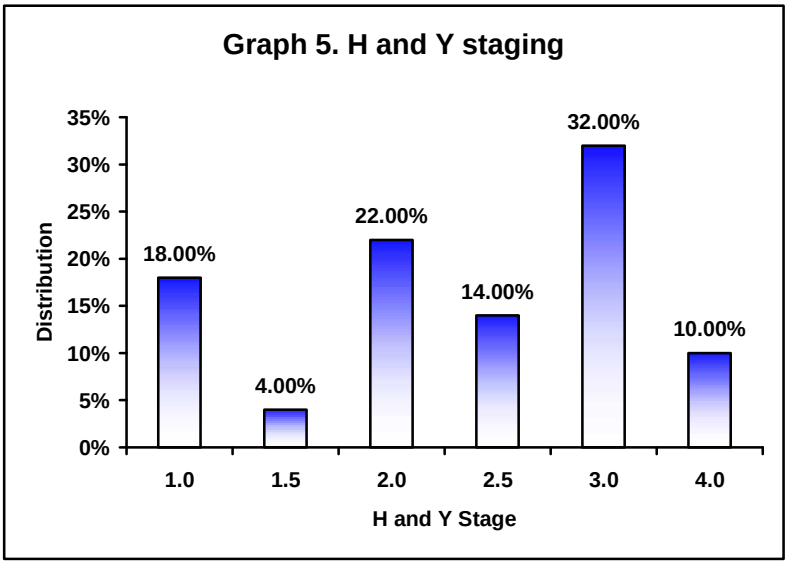
Duration (Years)	Distribution (n=50)	
	Number	Percent
< 1	25	50.00
1 to 3	16	32.00
4 to 6	8	16.00
7 to 9	0	0.00
> 9	1	2.00
Total	**50**	**100.00**



In our study, majority that is, 50% (n=25) of the patients, the duration of illness was less than 1 year. In 32% (n=16) of the patients the duration of illness was 1 to 3 years and the remaining had the disease for more than 3 years. The mean duration of illness was 2 years.

Table 5. H and Y staging

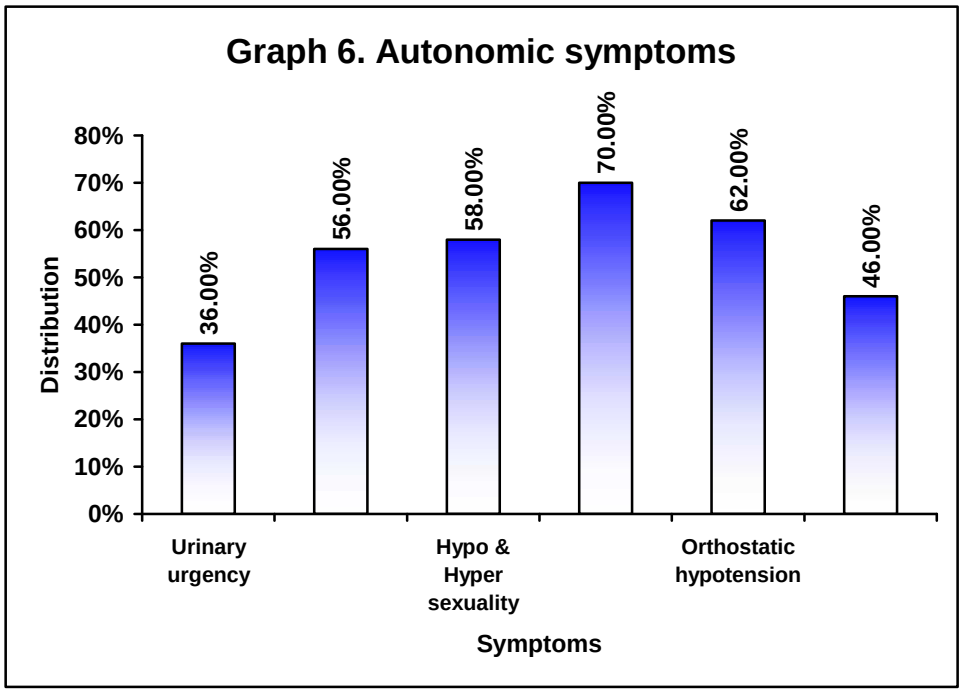
H & Y Stage	Distribution (n=50)	
	Number	**Percent**
1.0	9	18.00
1.5	2	4.00
2.0	11	22.00
2.5	7	14.00
3.0	16	32.00
4.0	5	10.00
Total	**50**	**100.00**



The above table shows the distribution of subjects according to H and Y staging for the disease. Majority of the patients belonged to H and Y stage 3.0 accounting for 32% (n=16), with 18% (n=9), 22% (n=11) and 14% (n=7) in stage 1.0, 2.0 and 2.5 respectively. Only 10% (n=5) belonged to stage 4.0 of the disease. The mean stage for the study subjects was 2.40±0.89 and median was 2.5

Table 6. Autonomic symptoms

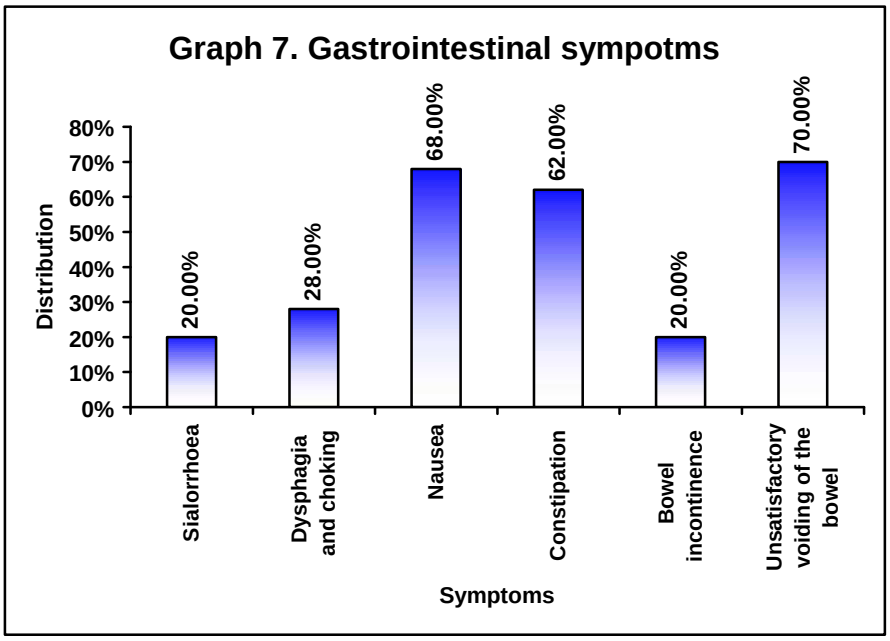
Symptoms	Distribution (n=50)	
	Number	**Percent**
Urinary urgency	18	36.00
Nocturia	28	56.00
Hypo and hypersexuality	29	58.00
Decreased libido	35	70.00
Orthostatic hypotension	31	62.00
Seborrhoea	23	46.00



In our study, among the autonomic symptoms studied, decreased libido was most common symptom i.e. 70% (n=35). Urinary urgency was least common symptom i.e. 36% (n=18).

Table 7. Gastrointestinal symptoms

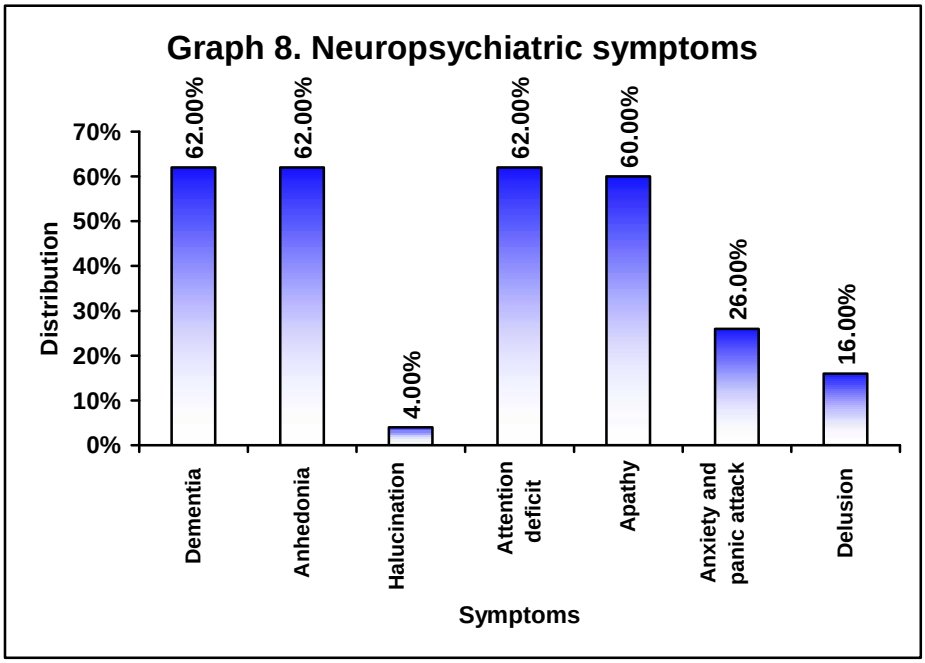
Symptoms	Distribution (n=50)	
	Number	**Percent**
Sialorrhoea	10	20.00
Dysphagia and choking	14	28.00
Nausea	34	68.00
Constipation	31	62.00
Bowel incontinence	10	20.00
Unsatisfactory voiding of the bowel	35	70.00



In our study, unsatisfactory voiding of the bowel was the most common gastro intestinal symptom accounting for 70% (n=35), with nausea, constipation next common symptoms with 68% (n=34) and 62% (n=31) respectively. Sialorrhoea and bowel incontinence was present in 20% (n=10) patients each.

Table 8. Neuropsychiatric symptoms

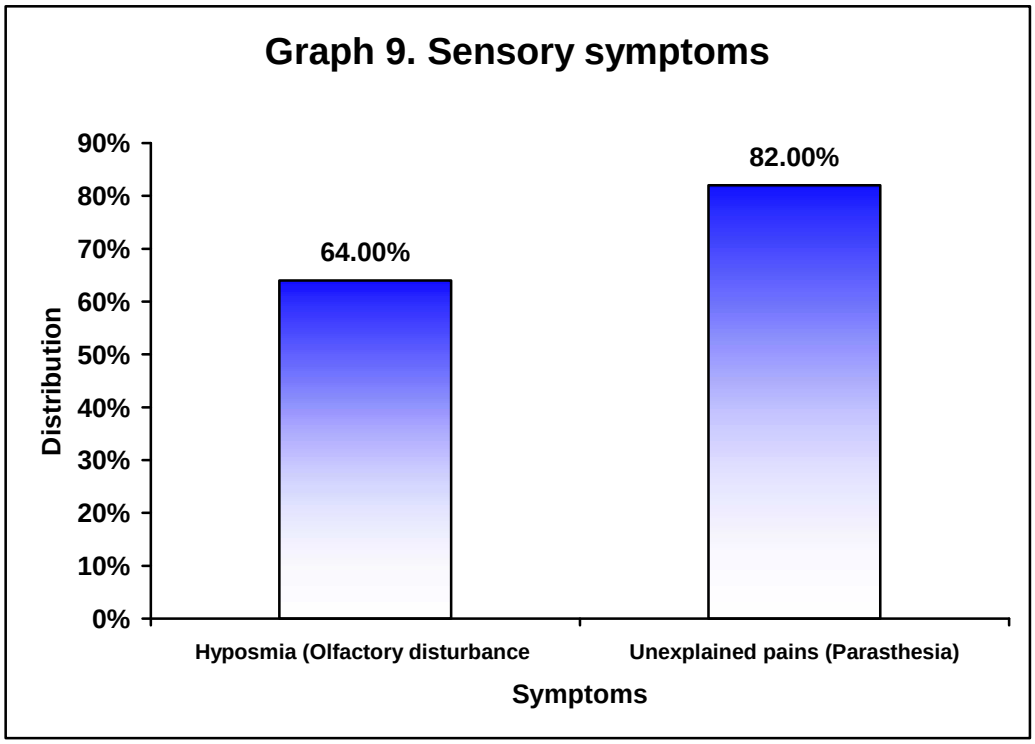
Symptoms	Distribution (n=50)	
	Number	Percent
Dementia	31	62.00
Anhedonia	31	62.00
Halucination	2	4.00
Attention deficit	31	62.00
Apathy	30	60.00
Anxiety and panic attack	13	26.00
Delusion	8	16.00



In our study, among the neuropsychiatric symptoms, dementia, anhedonia, and attention deficits were common symptoms with 62% (n=31) each. Delusion and hallucinations were present in 16% (n=8) and 4% (n=2) patients respectively.

Table 9. Sensory symptoms

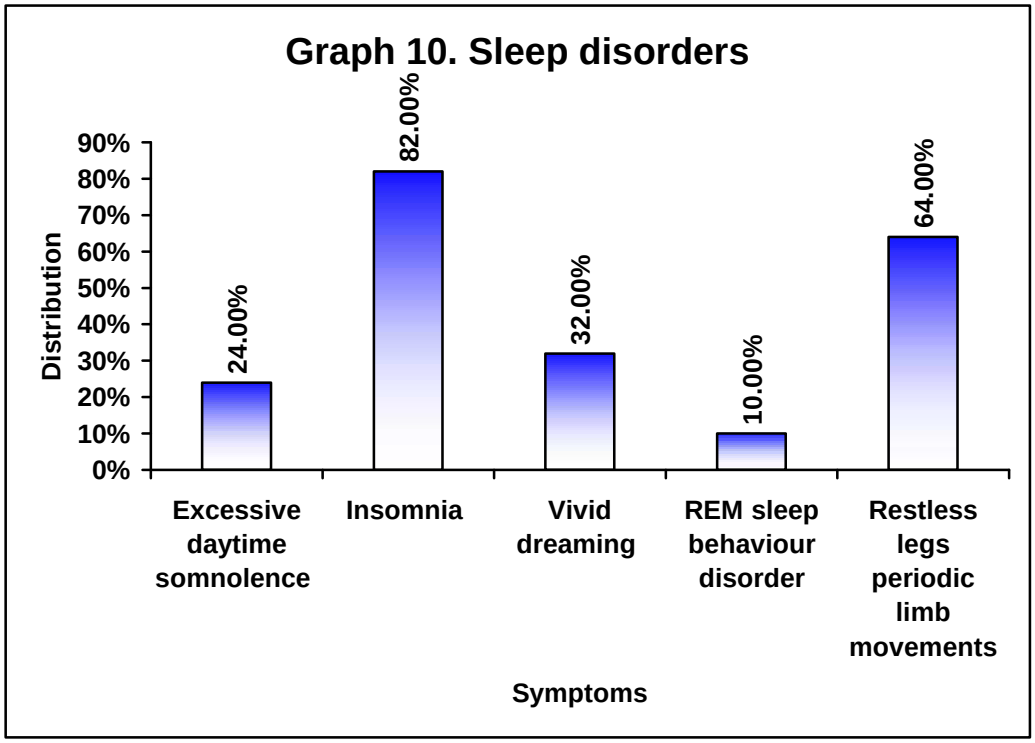
Symptoms	Distribution (n=50)	
	Number	Percent
Hyposmia (Olfactory disturbance)	32	64.00
Unexplained pains (Parasthesia)	41	82.00



In our study, olfactory disturbances and unexplained pains were present in 64% (n=32) and 82% (n=41) patients respectively.

Table 10. Sleep disorders

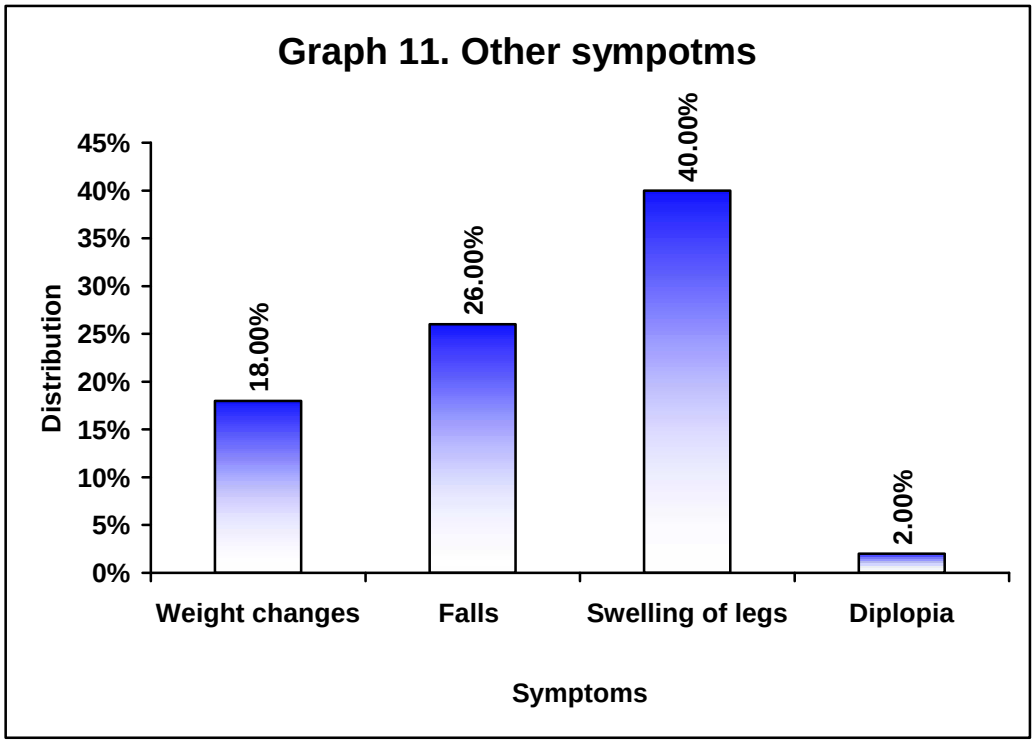
Symptoms	Distribution (n=50)	
	Number	**Percent**
Excessive daytime somnolence	12	24.00
Insomnia	41	82.00
Vivid dreaming	16	32.00
REM sleep behaviour disorder	5	10.00
Restless legs and periodic limb movements	32	64.00



In this study, insomnia was most prevalent symptom that is, 82% (n=41) among sleep disorders, followed by symptom of restless legs and periodic limb movement which was observed in 64%(n=32) of patients. Excessive daytime somnolence and vivid dreaming was present in 24%(n=12) and 32%(n=18) respectively.

Table 11. Other symptoms

Symptoms	Distribution (n=50)	
	Number	Percent
Weight changes	9	18.00
Falls	13	26.00
Swelling of legs	20	40.00
Diplopia	1	2.00



Among the other symptoms in our study, weight changes and swelling of the legs were present in 18% (n=9) and 40% (n=20) of patients respectively. 26% (n=13) had symptoms of fall. Diplopia was least common symptom is the study and was present in only 1 patient.

Chapter 6

Discussion

DISCUSSION

Parkinson's disease (PD) is the second most common neurodegenerative disorder, after Alzheimer's disease. The cardinal clinical features of PD include asymmetric onset of bradykinesia, rigidity, and resting tremor. Most patients of idiopathic PD present with one or more of the cardinal motor features.

Apart from these, various nonmotor symptoms (NMS) also occur in PD and constitute a major clinical challenge, as they are common, but often overshadowed by the dominance of motor symptoms. Non-motor symptoms are sources of considerable burden in people with PD, especially in elderly patients. The usual non-motor symptoms include cognitive declines, psychiatric disturbances (depression, psychosis, impulse control), autonomic failures (gastrointestinal, cardiovascular, urinary, sexual ability, thermoregulation), sleep difficulties, and pain syndrome. NMS can present at any stage of the disease including early and pre-motor phase of PD. Several NMS such as olfactory dysfunction, constipation, REM behavior disorder, depression may antedate the motor signs, symptoms and diagnosis of PD by a number of years.

Since, NMS add significantly to the overall disability caused by PD, their early recognition and treatment may go a long way in improving the quality of life of PD patients as well as the economic burden on the careers. The identification of NMS can be improved by the application of quantitative and validated instruments and scales for their assessment.

The present study was undertaken to study the clinical profile of non motor symptoms in patients with PD, with the primary objective to know the

prevalence of non motor symptoms in patients with PD and to classify and analyse the NMS on basis of systems involved.

This one year cross sectional study was conducted in the Department of Medicine, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum on patients with PD. A total of 50 patients diagnosed with Parkinson's disease were selected for the study.

In this study, demographic data such as age, sex and education were recorded. Patients were asked for the history regarding other neurological illness, duration and medications. Further thorough clinical examination was conducted.

The diagnosis of Parkinson's disease was confirmed by UKPDS Brain Bank Criteria. Neurological examination was conducted for MMSE scores and H and Y staging. The patients were provided with NMS Questionnaire to assess of non motor symptoms and the results were analysed.

In our study of the 50 patients studied, 56% (n=28) were males and 44% (n=22) were females. Several studies done in the past have also showed higher prevalence of PD in the males compared to the females. One meta-analysis[30] based on 17 incidence studies of PD reported a pooled age-adjusted male to female ratio of 1.46. In our study male to female ratio was 1.27. Some studies did not find any gender differences.

In our study it was observed that highest number of patients (32%) belonged to the age group of 61-70 years. The next highest number of patients belonged to the age group of 40-50 years (30%) and 51-60 years (30%). Only 8%

of the patients were aged above 70 years. The mean age of the study population was 57.92±9.03 with median age of 58.5 years.

These results were in line with other incidence studies, prevalence of PD clearly increases with age. However, some studies[26,32] reported a decline in prevalence in the oldest age group (above 80 or more) perhaps due to underdiagnosis of PD because of comorbidity,[92] non-response,[93] and unstable estimates due to small numbers in old age groups.

In other studies, there are no or very few cases occurring before 40 years. Also, the incidence of PD clearly increases with age steeply after age 60. However, several studies reported that incidence rates dropped in older age groups.[22] It is still a matter of debate whether this decline is real or due to underdiagnosis. However our study also reported similar finding.

In our study of the total 50 patients, 60 % (n=30) were newly diagnosed patients of Parkinson's disease with varying duration of illness but not on treatment. The remaining 40% (n=20) were known patients of Parkinson's disease of varying duration of illness on treatment particularly on levodopa therapy.

In our study, majority i.e 50% (n=25) of the patients, the duration of illness was less than 1 year. In 32%(n=16) of the patients the duration of illness was 1 to 3 years and the remaining had the disease for more than 3 years of which 8 patient had duration of illness ranging from 4 to 6 years and in one patients duration of illness was 10 years. The mean duration of illness in our study was 2 years.

In our study, majority of the patients belonged to H and Y stage 3.0 accounting for 32% (n=16), with 18% (n=9), 22% (n=11) and 14% (n=7) in stage 1.0, 2.0 and 2.5 respectively. Only 10% (n=5) belonged to stage 4.0 of the disease. There were no patients in stage 0 and stage 5 of the PD in our study. The mean stage for the study subjects was 2.40±0.89 and median was 2.5 symptoms.

In the present study the mean number of non motor symptoms was 13.2 ± 3.55 and median number of symptom was 13 with range of 5 being minimum and 20 being maximum. Further, as the stage of the disease increased the mean number of non motor symptoms increased from 10.11 ± 3.22 in grade 1 to 17.2 ± 1.79 in grade 4 except grade 1.5 where the mean was 9.00 ± 4.24 which could be attributed to the only two patients in this group.

In our study, analyzing the NMS according to the systems involved, all the five autonomic symptoms studied were present in study group in various proportions. Decreased libido was most the autonomic common symptom that is, 70% (n=35). Urinary urgency was the least common symptom that is, 36% (n=18). Nocturia, hypo and hypersexuality, orthostatic hypotension and seborrhea were present in 56% (n=28), 58% (n=29), 62% (n=31) and 46% (n=23) patients respectively.

Yu and colleagues[70] noted that 17 of 21 (80%) male patients with PD had substantial impairment of sexual arousal, behaviour, drive, and orgasm domains, whereas in those with longer duration of the disease sexual fantasy was increased. Another study reported high prevalence (76.5%) of sexual dysfunction in patients after bilateral subthalamic nucleus stimulation80 .In the study by Kelly Lyons

and Lyons K et al[94] in 2011 urinary disturbances were present in 60% of the study group.

In a study by Senard JM et al[66] showed the presence of orthostatic hypotension in 58% patients which was similar to results of our study.

In our study, among the gastro intestinal symptoms studied in 50 patients, unsatisfactory voiding of the bowel was the most common gastro intestinal symptom accounting for 70% (n=35), with nausea, constipation next common symptoms with 68% (n=34) and 62% (n=31) respectively. Symptoms of dysphagia were present in 28% (n=14) patients of our study. Sialorrhoea and bowel incontinence was present in 20% (n=10) patients each.

In study by Lyons K et al[94] in 2011, constipation was experienced by upto 60% of the study group. Several case control studies have reported increased prevalence of constipation in PD of between 28% and 61% compared to control cases (6%-33%). Jost WH[68] reported either constipation or prolonged intestinal transit time in as many as 80% of patients with PD. Constipation has been reported as a prominent complaint prior to the onset of motor symptoms of PD in about 50% of patients in one series by Korczyn AD.[67]

In our study, among the neuropsychiatric symptoms, dementia, anhedonia, and attention deficits were the common symptoms with 62% (n=31) each. Symptoms of delusion and hallucinations were present in 16% (n=8) and 4% (n=2) patients respectively. Symptoms suggestive of apathy and anxiety were present in 60% (n=30) and 26% (n=13) patients respectively.

In a study by Emre M[84] Dementia occurs in up to 40% of people with PD, a rate about six-times higher than that in healthy individuals 64. The prevalence of major depression in PD is estimated to be 40%.[29] with reported prevalence rates ranging from 4% to 70%. Richard IH et al[95] reported clinically significant anxiety syndromes occur in upto 40% of patients with PD. Other study demonstrated prevalence of panic attacks in upto 25% patients. A study by Goetz CG et al.[12] reported hallucinations and delusions occur in up to 40% of PD patients and are a major precipitant of nursing home placement.

The results of our study for the neuropsychiatric symptoms were comparable to the results of the other studies except that the prevalence of symtoms of hallucination and delusion were lower in our study.

In our study, sensory symptoms of olfactory disturbances and unexplained pains were present in 64% (n=32) and 82% (n=41) patients respectively.

However previous studies have reported primary sensory symptoms in 40%-50% of patients[12]. Olfactory disturbances were prevalent in about 80%-90% of the patients in several previous studies and are one of the earliest and preclinical markers of PD. The low prevalence of olfactory disturbance in our study may be due to under reporting of this symptom by the patients and while the other studies used more sensitive smell identification test for the odour identification, discrimination and detection.

In this study, insomnia was the most prevalent symptom that is 82% (n=41) among sleep disorders, followed by the symptom of restless legs and periodic limb movement which was observed in 64%(n=32) of patients.

Excessive daytime somnolence and vivid dreaming was present in 24% (n=12) and 32% (n=18) respectively. REM sleep behavior disorder was observed in 10% (n=5) patients in our study.

In study by Lyons K et al[94] reported 98% prevalence of sleep disturbances in patients with PD which was comparable with our study results. Abbott RD et al[97] reported excessive day time sleepiness affected up 50% of patients and may also be preclinical marker for PD.

In the study by Chauduri KR et al[97] , daytime sleepiness, insomnia, vivid dreams and restless legs were reported in 31%,33%,45% and 41% patients respectively.

Among the other symptoms in our study, weight changes and swelling of the legs were present in 18% (n=9) and 40% (n=20) of patients respectively. 26% (n=13) had symptoms of fall. Diplopia was least common symptom is the study and was present in only 1 patient.

Our results were comparable to the results published by Chuadhuri KR et al[97] published in 2007 in which weight changes, swelling and falls were present in 18.29%, 31.30% and 28% of the study subjects. However diplopia was present in 20% of patients in above study.

Chapter 7

Conclusion

CONCLUSION

- The non motor symptoms were universally prevalent in all the patients with Parkinson's disease.
- The number of non motors symptoms increased as the stage of the Parkinson's disease progressed.
- Insomnia and unexplained pains were the most prevalent non motor symptoms.

Chapter 8

Summary

SUMMARY

The nonmotor symptoms are universal features of idiopathic PD. They add significantly to the overall disability caused by PD and are the critical determinants of health related quality of life of affected patients. NMS can present at any stage of the disease including early and pre-motor phase of PD.

The present study was undertaken to study the clinical profile of non motor symptoms in patients with PD, with the primary objective to know the prevalence of non motor symptoms in patients with PD and to classify and analyse the NMS on basis of systems involved.

In the present study, prevalence of PD was more in the males compared to the females. The mean age of the study population was 57.92±9.03 with median age of 58.5 years and the mean duration of illness in our study was 2 years.

Analysing the NMS, they were universally present in all PD patients in varying number, and mean number of NMS among the study subjects was 13.2±3.55.The majority of the patients belonged to H and Y stage 3.0 and further, as the stage of the disease increased the mean number of non motor symptoms increased.

Decreased libido was the most common autonomic symptom among PD patients. Orthostatic Hypotension was present in 56% of study subjects. Among the gastro intestinal symptoms studied, unsatisfactory voiding of the bowel was the most common gastro intestinal symptom accounting for 70% (n=35) followed by nausea and constipation.

In our study, dementia, anhedonia, and attention deficits were common neuropsychiatric symptoms with 62% (n=31) each. Sensory symptoms of olfactory disturbances and unexplained pains were present in 64% (n=32) and 82% (n=41) patients respectively. Insomnia was most prevalent symptom that is, 82% (n=41) among sleep disorders, followed by symptom of restless legs and periodic limb movement which was observed in 64% (n=32) of patients.

Diplopia was the least common symptom is the study and was present in only 1 patient.

In the presence of effective symptomatic therapies for the motor symptoms of PD, the non motor symptoms have become major prognostic factors for overall disease burden and everyday function in PD.

Furthermore, there is evidence that many nonmotor symptoms may antedate the onset of motor symptoms of PD by years and may thus turn out to be a critical target for early diagnosis and identification of at-risk populations.

Early recognition and treatment of nonmotor symptoms may go a long way in improving the quality of life of PD patients as well as the economic burden on the careers.

Chapter 9

Bibliography

BIBLIOGRAPHY

1. Nussbaum RL, Ellis CE. Alzheimer's disease and Parkinson's disease. NEJM 2003;348(14):1356-64.

2. Mutch WJ, Dingwall-Fordyce I, Downie AW, Paterson JG, Roy SK. Parkinson's disease in a Scottish City. BMJ 1986;292:534-6.

3. Behari M. Treatment of Parkinson's disease: fighting the surging enemy. Neurol India 1999;47:259-62.

4. de Lau Lm, Breteler mm. Epidemiology of Parkinson's disease. Lancet Neurol 2006;5:525-35.

5. Mitra K, Gangopadhyaya PK, Das SK. Parkinsonism plus syndromes - A review. Neurology India 2003;5:183-8.

6. DeLong mR, Juncos JL. Parkinson's disease and other extrapyramidal movement disorders. In: Fauci AS, Braunwald E, Kasper DL, Hauser SL, Longo DL, Jameson JL, et al., eds. Harrison's principles of internal medicine 17th ed. New York (Ny): The mcGraw-Hill Companies 2008; p. 2549-59.

7. Davie CA. A review of Parkinson's disease. Br Med Bull 2008;86(1):109-27.

8. Hauser RA. Parkinson disease. 2012 Available from: URL:http://emedicine.medscape.com/article/1831191-overview Access Date:05.05.2012.

9. Barone P, Antonini A, Colosimo C, Marconi R, Morgante L, Avarello TP, et al. The PRIAMO study:a multicenter assessment of nonmotor symptoms and their impact on quality of life in Parkinson's disease. Movement Disorders, 2009;24(11):1641–9.

10. Chaudhuri KR, Prieto-Jurcynska C, Naidu Y, Mitra T, Frades-Payo B, Tluk S, et al. The nondeclaration of nonmotor symptoms of Parkinson's disease to health care professionals:an international study using the nonmotor symptoms questionnaire. Movement Disorders 2010;25(6):697–701.

11. Chaudhuri KR, Schapira AH. Non-motor symptoms of Parkinson's disease: dopaminergic pathophysiology and treatment. The Lancet Neurology 2009;8(5):464–74.

12. Goetz CG. The History of Parkinson's Disease: Early Clinical Descriptions and Neurological Therapies. Cold Spring Harb Perspect Med 2011;1(1):a008862.

13. Hoehn MM, Yahr MD 1967. Parkinsonism: Onset, progression and mortality. Neurology 17:427–442.

14. Muangpaisan W, Mathews A, Hori H, Seidel D. A systematic review of the worldwide prevalence and incidence of Parkinson's disease. J Med Assoc Thai. 2011;94(6):749-55.

15. de Rijk MC, Launer LJ, Berger K, Breteler MM, Dartigues JF, Baldereschi M, et al. Prevalence of Parkinson's disease in Europe: A

collaborative study of population- based cohorts. Neurologic Diseases in the Elderly Research Group. Neurology 2000;54:S21-3.

16. de Rijk MC, Tzourio C, Breteler MM, Dartigues JF, Amaducci L, Lopez-Pousa S, et al. Prevalence of parkinsonism and Parkinson's disease in Europe: the EUROPARKINSON Collaborative Study. European Community Concerted Action on the Epidemiology of Parkinson's disease. J Neurol Neurosurg Psychiatry. 1997;62:10-5.

17. Zhang ZX, Roman GC, Hong Z, Wu CB, Qu QM, Huang JB, et al. Parkinson's disease in China: Prevalence in Beijing, Xian, and Shanghai. Lancet. 2005;365:595-7.

18. Hirtz D, Thurman DJ, Gwinn-Hardy K, Mohamed M, Chaudhuri AR, Zalutsky R. How common are the "common" neurologic disorders? Neurology. 2007;68:326-37.

19. Dorsey ER, Constantinescu R, Thompson JP, Biglan KM, Holloway RG, Kieburtz K, et al. Projected number of people with Parkinson disease in the most populous nations, 2005 through 2030. Neurology. 2007;68:384-6.

20. Zhang ZX, Roman GC. Worldwide occurrence of Parkinson's disease: an updated review. Neuroepidemiology 1993;12:195-208.

21. Barbosa MT, Caramelli P, Maia DP, Cunningham MC, Guerra HL, Lima-Costa MF, et al. Parkinsonism and Parkinson's disease in the

elderly: A community-based survey in Brazil (the Bambui study). Mov Disord 2006;21:800-8.

22. Chen RC, Chang SF, Su CL, Chen TH, Yen MF, Wu HM, et al. Prevalence, incidence, and mortality of PD: A door-to-door survey in Ilan county, Taiwan. Neurology 2001;57:1679-86.

23. Driver JA, Logroscino G, Gaziano JM, Kurth T. Incidence and remaining lifetime risk of Parkinson disease in advanced age. Neurology. 2009;72:432-8.

24. Taylor KS, Counsell CE, Harris CE, Gordon JC, Smith WC. Pilot study of the incidence and prognosis of degenerative Parkinsonian disorders in Aberdeen, United Kingdom: Methods and preliminary results. Mov Disord. 2006;21:976-82.

25. Van Den Eeden SK, Tanner CM, Bernstein AL, Fross RD, Leimpeter A, Bloch DA, et al. Incidence of Parkinson's disease: Variation by age, gender, and race/ethnicity. Am J Epidemiol 2003;157:1015-22.

26. Wang YS, Shi YM, Wu ZY, He YX, Zhang BZ. Parkinson's disease in China. Coordinational Group of Neuroepidemiology, PLA. Chin Med J (Engl) 1991;104:960-4.

27. de Lau LM, Giesbergen PC, de Rijk MC, Hofman A, Koudstaal PJ, Breteler MM. Incidence of parkinsonism and Parkinson disease in a general population: the Rotterdam Study. Neurology. 2004;63:1240-4.

28. Tan LC, Venketasubramanian N, Jamora RD, Heng D. Incidence of Parkinson's disease in Singapore. Parkinsonism Relat Disord. 2007;13:40-3.

29. Mayeux R, Marder K, Cote LJ, Denaro J, Hemenegildo N, Mejia H, et al. The frequency of idiopathic Parkinson's disease by age, ethnic group, and sex in northern Manhattan, 1988-1993. Am J Epidemiol. 1995;142:820-7.

30. Wooten GF, Currie LJ, Bovbjerg VE, Lee JK, Patrie J. Are men at greater risk for Parkinson's disease than women? J Neurol Neurosurg Psychiatry. 2004;75:637-9.

31. Taylor KS, Cook JA, Counsell CE. Heterogeneity in male to female risk for Parkinson's disease. J Neurol Neurosurg Psychiatry. 2007;78:905-6.

32. Benito-Leon J, Bermejo-Pareja F, Rodriguez J, Molina JA, Gabriel R, Morales JM. Prevalence of PD and other types of parkinsonism in three elderly populations of central Spain. Mov Disord 2003;18:267-74.

33. de Rijk MC, Rocca WA, Anderson DW, Melcon MO, Breteler MM, Maraganore DM. A population perspective on diagnostic criteria for Parkinson's disease. Neurology. 1997;48:1277-81.

34. Elbaz A, Bower JH, Maraganore DM, McDonnell SK, Peterson BJ, Ahlskog JE, et al. Risk tables for parkinsonism and Parkinson's disease. J Clin Epidemiol. 2002;55:25-31.

35. Ishihara LS, Cheesbrough A, Brayne C, Schrag A. Estimated life expectancy of Parkinson's patients compared with the UK population. J Neurol Neurosurg Psychiatry. 2007;78:1304-9.

36. Muthane UB, Ragothaman M, Gururaj G. Epidemiology of Parkinson's disease and movement disorders in India:problems and possibilities. J Assoc Physicians India. 2007;55:719-24.

37. Bharucha NE, Bharucha EP, Bharucha AE, Bhise AV, Schoenberg BS. Prevalence of Parkinson's disease in the Parsi community of Bombay, India. Arch Neurol 1988;45:1321-3.

38. Bharucha NE, Bharucha EP, Dastur HD, Schoenberg BS. Pilot survey of the prevalence of neurologic disorders in the Parsi community of Bombay. American Journal of Preventive Medicine 1987;3:299.

39. Anand KS, Singh MM. Pattern of neurological disorders above the middle aged population in JIPMER, Pondicherry. Neurology India 1993;41:165-8.

40. Ragothaman M, Murgod UA, Gururaj G, Louis ED, Subbakrishna DK, Muthane U. High occurrence and low recognition of Parkinson's disease in Elderly Homes in Bangalore, India: Implications for healthcare of elderly. Movement Disorders. 2006.

41. Razdan S, Kaul RL, Motta A, Kaul S, Bhatt RK. Epidemiology of Neurological disorders in Kashmir. Neuroepidemiology 1994;13:113-9.

42. Das SK, Sanyal K. Neuroepidemiology of major neurological disorders in rural Bengal. Neurology India 1996;44:47-58.

43. Fauci AS, Kasper DS, Longo DL, Braunwald E, Hauser SL, Jameson JL, et al. Harrison's principles of internal medicine. United States; McGraw Hill: 2008.

44. Braak H, Del Tredici K, Rub U, de Vos, RA, Jansen Steur EN, Braak E. Staging of brain pathology related to sporadic Parkinson's disease. Neurobiol Aging 2003;24:197-211.

45. Vila M, Vukosavic S, Jackson-Lewis V, Neystat M, Jakowec M. Przedborski S. Alpha-synuclein up-regulation in substantia nigra dopaminergic neurons following administration of the parkinsonian toxin MPTP. J Neurochem 2000;74:721-9.

46. Hatano T, Hattori N. Etiology and Pathogenesis of Parkinson's Disease. Tokyo**:** Juntendo University School of Medicine; 2010.

47. Jankovic J. Parkinson's disease: Clinical features and diagnosis. J Neurol Neurosurg Psychiatry. 2008;79(4):368-76.

48. Brodsky H, Dat Vuong K, Thomas M, Jankovic J. Glabellar and palmomental reflexes in Parkinsonian disorders. Neurology 2004;63:1096–8.

49. Weerkamp NJ, Nijhof A, Tissingh G. Non-motor symptoms of Parkinson's disease. Ned Tijdschr Geneeskd. 2012;156(8):A3926.

50. Mehndiratta M, Garg RK, Pandey S. Nonmotor symptom complex of Parkinson's disease--an under-recognized entity. J Assoc Physicians India. 2011;59:302-8, 313.

51. Chaudhuri KR, Naidu Y. Early Parkinson's disease and non-motor issues. J Neurol 2008;255:33-8.

52. Stacy M, Bowron A, Guttman M, Hauser R, Hughes K, Larsen JP, et al. Identification of motor and non motor wearing off in Parkinson's disease:comparison of a patient questionnaire versus a clinician assessment. Mov Disord 2005;20:726-33.

53. Chaudhuri KR, Martinez-Martin P, Brown RG, Sethi K, Stocchi F, Odin P,et al. The metric properties of a novel non-motor symptoms scale for Parkinson's disease: Results from an international pilot study. Mov Disord 2007;22:1901-11.

54. Chaudhuri KR, Healy DG, Schapira AHV. Non-motor symptoms of Parkinson's disease: Diagnosis and management. Lancet Neurol 2006;5:235-45.

55. Ahlskog JE. Challenging conventional wisdom: The etiologic role of dopamine oxidative stress in Parkinson's disease. Mov Disord 2005;20:271-82.

56. Braak H, Del Tredici K, Rüb U, de Vos RAI, Jansen Steur ENH, Braak E. Staging of brain pathology related to sporadic Parkinson's disease. Neurobiol Aging 2003;24:197-210.

57. Del Tredici K, Braak H. Idiopathic Parkinson's disease:staging an α - synucleinopathy with a predictable pathoanatomy. In: Kahle P, Haass C, eds. Molecular mechanisms in Parkinson's disease. Georgetown, TX: Landes Bioscience;2004;1-32.

58. Tandberg E, Larsen JP, Karlsen K. A community-based study of sleep disorders in patients with Parkinson's disease. Mov Disord 1998;13:895-9.

59. Poewe W. Nonmotor symptoms in Parkinson's disease. In:Jankovic J, Tolosa E, eds. Parkinson's disease and movement disorders 5th ed. Philadelphia: Lippincott Williams and Wilkins; 2007. p. 67-76.

60. Poewe W, Hogl B. Akathisia, restless legs and periodic limb movements in sleep in Parkinson's disease. Neurology 2004;63:12-6.

61. Starkstein SE, Mayberg HS. Depression in Parkinson's disease, In: Starkstein SE, Robinson RG eds. Depression in neurologic disease. Baltimore, MD: Johns Hopkins University Press; 1993. p. 97-116.

62. Magerkurth C, Schnitzer R, Braune S. Symptoms of autonomic failure in Parkinson's disease: Prevalence and impact on daily life. Clin Auton Res 2005;15:76-82.

63. Chaudhuri KR, Martinez-Martin P, Schapira AHV, Stocchi F, Sethi K, Odin P, et al. International multicenter pilot study of the first comprehensive self-completed nonmotor symptoms questionnaire for Parkinson's disease: The NMSQuest Study. Mov Disord 2006;21:916-23.

64. Bannister R, Mathias CJ. Clinical features and evaluation of primary chronic autonomic failure syndromes. In: Mathias CJ, Bannister R, eds. Autonomic failure, 4th edn. Oxford, UK: Oxford University Press; 1999. p. 307–16.

65. Magalhaes M, Wenning GK, Daniel SE, Quinn NP. Autonomic dysfunction in pathologically confirmed multiple system atrophy and idiopathic Parkinson's disease:a retrospective comparison. Acta Neurol Scand 1995;91:98-102.

66. Senard JM, rai S, Lapeyre-Mestre M, Brefel C, Rascol O, Rascol A, et al. Prevalence of orthostatic hyotension in Parkinson's disease. J Neurol Neurosurg Psychiatry 1997;63:584-9.

67. Korczyn AD. Autonomic nervous system disturbances in Parkinson's disease. Adv Neurol 1990;53:463-8.

68. Jost WH. Gastrointestinal motility problems in patients with Parkinson's disease: Effects of antiparkinsonian treatment and guidelines for management. Drugs Aging 1997;10:249-58.

69. Den Hartog Jager WA, Bethlem J. the distribution of Lewy bodies in the central and autonomic nervous system in idiopathic paralysis agitans. J Neurol Neurosurg Psychiatry 1960;23:283-90.

70. Yu M, Roane DM, Miner CR, Fleming F, Rogers JD. Dimensions of sexual dysfunction in Parkinson Disease. Am J Geriatr Psychiatry 2004;12:221-6.

71. Pezzella FR, Colosimo C, Vanacore N, et al. Prevalence and clinical features of hedonistic homeostatic dysregulation in Parkinson's disease. Mov Disord 2005;20:77-81.

72. Shulman LM, Taback RL, Rabinstein AA, Weiner WJ. Nonrecognition of depression and other non-motor symptoms in Parkinson's disease. Parkinsonism Relat Disord 2002;8:193-7.

73. Chaudhuri KR, Healy DG, Schapira AHV. Non-motor symptoms of Parkinson's disease: Diagnosis and management. Lancet Neurol 2006;5:235-45.

74. Goetz CG, Tanner CM, Levy M, Wilson RS, Garron DC. Pain in Parkinson's disease. Mov Disord 1986;1:45-9.

75. Schott GD. Pain in Parkinson's disease. Pain 1985;22:407-11.

76. Buzas B, Max MB. Pain in Parkinson's disease. Neurology 2004;62:2156-67.

77. Poewe W. Nonmotor symptoms in Parkinson's disease. In: Jankovic J, Tolosa E, eds. Parkinson's disease and movement disorders 5th ed. Philadelphia: Lippincott Williams and Wilkins; 2007. p. 67-76.

78. Siderowf A, Jdennings D, Connolly J, Doty R, Mareck K, Stern M. Risk factors for Parkinson's disease and impaired olfaction in relatives of patients with Parkinson's disease. Mov Disord 2007;22:2249-55.

79. Ross W, Petrovitch H, Abbott RD, Tanner CM, Popper J, Masaki K, et al. Association of olfactory dysfunction with risk of future Parkinson's disease. Mov Disord 2005;20:P439

80. Corrigan MH, Denahan AQ, Wright CE, Ragual RJ, Evans DL:Comparison of pramipexole, fluoxetine, and placebo in patients with major depression. Depress. Anxiety 11(2), 58–65 (2000).

81. Singh A, Althoff R, Martineau RJ, Jacobson J: Pramipexole, ropinirole and mania in Parkinson's disease. Am. J. Psychiatry 162(4), 814–815 (2005).

82. Factor SA, Friedman JH, Lannon MC, Oakes D, Bourgeois K, Parkinson Study Group: Clozapine for treatment of drug induced psychosis in Parkinson's disease: Results of the 12-week open label extension in the PSYCLOPS trial. Mov. Disord. 2001;16:135–9.

83. Ondo WG, Tintner R, Vuong Dat K, Lai D, Ringholz G. Double blind placebo controlled unforced titration parallel trial of quetiapine for dopaminergic-induced hallucinations in Parkinson's disease. Mov. Disord 2005;20:958–63.

84. Emre M, Aarsland D, Albanese A, Byrne EJ, Deuschl G, De Deyn PP, et al. Rivastigmine for dementia associated with Parkinson's disease. N. Eng. J. Med. 2004;351:2509–18.

85. Ravina B, Putt M, Siderowf A, Farrar JT, Gillespie M, Crawley A, et al. Donezepil for dementia in Parkinson's disease:a randomised double

blind, placebo controlled, crossover study. J. Neurol. Neurosurg. Psychiatry 2005;76(7):934–9.

86. Adler CH, Caviness JN, Hentz JG et al.:Randomised trial of modafinil for treating subjective daytime sleepiness in patients with Parkinson's disease. Mov. Disord 2003;18:287–93.

87. Ondo WG, Fayle R, Atassi F, Jankovic J:Modafinil for daytime somnolence in Parkinson's disease: Double blind, placebo controlled parallel trial. J. Neurol. Neurosurg. Psychiatry 2005;76(12):1636–9.

88. Lagalla G, Millevolte M, Capecci M, Provinciali L, Ceravolo MG. Botulinum toxin type A for drooling in Parkinson's disease:a double blind, randomized,placebo-controlled study. Mov. Disord 2006;21:704–7.

89. Eichhorn TE, Oertel WH:Macrogol 3350/electrolyte improves constipation in Parkinson's disease and multiple system atrophy. Mov. Disord. 2001;16:1176–7.

90. Kalteis K, Standhartdt H, Kryspin-Exner I, Brucke T, Volt D, Ales F:Influence of bilateral Stn-stimulation on psychiatric symptoms and psychosocial functioning in patients with Parkinson's disease. J. Neural Transm. 2005;113(9):1191–206.

91. Castelli L, Perozzo P, Zibetti M, Crivelli B, Morabito U, Lanotte M, et al. Chronic deep brain stimulation of the subthalamic nucleus for Parkinson's disease: Effects on cognition, mood, anxiety and personality traits. Eur. Neurol. 2006;55(3):136–44.

92. Bower JH, Maraganore DM, McDonnell SK, Rocca WA. Influence of strict, intermediate, and broad diagnostic criteria on the age- and sex-specific incidence of Parkinson's disease. Mov Disord. 2000;15:819-25.

93. Anderson DW, Rocca WA, de Rijk MC, Grigoletto F, Melcon MO, Breteler MM, et al. Case ascertainment uncertainties in prevalence surveys of Parkinson's disease. Mov Disord. 1998;13:626-32.

94. Lyons KE, Pahwa R. The impact and management of nonmotor symptoms of Parkinson's disease. Am J Manag Care 2011;17(12):S308-14.

95. Richard IH, Schiffer RB, Kurlan R. Anxiety and Parkinson’s disease. J Neuropsychiatry Clin Neurosci 1996;8:383-92.

96. Abbott RD, Ross GW, White LR, Tanner CM, Nelson JS, Petrovicth H, et al. Excessive daytime sleepiness and the future risk of Parkinson’s disease. Mov Disord 2005;20(10):S101.

97. Chaudari KR, Martinez-Martin P, Schapira AHV, Schapira AH, Stocchi F, Sethi K, Odin P. et al. International Multi Centre Pilot Study of the First Comprehensive Self completed Nonmotor Symptoms Questionnaire for Parkinson's Disease: The NMS Quest Study. Mov Disord 2006;21:916-23

Annexures

Annexure I

ANNEXURE I – CONSENT FORM

"A CLINICAL PROFILE OF NON MOTOR SYMPTOMS IN PARKINSON'S DISEASE" ONE YEAR CROSS SECTIONAL STUDY AT DR. PRABHAKAR KORE HOSPITAL AND MEDICAL RESEARCH CENTRE.

Principal Investigator: **Dr. **** ********

Guide: **Dr. ***** ********

VOLUNTARY PARTICIPATION / WITHDRAWAL

Taking part in this study is voluntary. I may choose not to take part in this study, or if I decide to take part I can later change my mind and withdraw from the study. My decision is will not change the present or future health care or other services that I receive. The study doctor or sponsor may stop my participation in this study any time. If I choose not to take part in the study I will receive the standard treatment for patients with my condition.

COSTS: Costs for investigations : Nil

COMPENSATION The study is purely voluntary and no compensation will be given in any form.

CONFIDENTIALITY

All information collected about me during the course of this study will be kept confidential to the extent permitted by law. The code numbers will identify me in this research record. Information from this study may be published but my identity will be confidential in any publication. This research is intended to study the clinical analysis of non-motor symptoms of Parkinson's disease. I agree to be part of the study and hence requested to participate in the same.

If I agree to be part of the research study I will be asked the relevant history and will be subjected to relevant clinical examination. My co-operation will be of great help to people who have Parkinsons disease in understanding their various non-motor symptoms.

CONSENT OF THE SUBJECT TO PARTICIPATE IN THE STUDY

I voluntarily agree to take part in this study by signing below. I may withdraw at any time. I am not giving up any of my legal rights by signing this form. My signature below indicates that I have read, or it has been read to me, this entire consent form, and have had all my questions answered.

Name of the Participant or legally authorised representative:

_____

Signature _____

In case of the queries during study or in future you may contact following person

Principal investigator: Dr. **** *****

Guide: Dr. ***** ****

Name of the legally authorised representative

_____

Signature _____

Name of the Witness _____

Signature _____

Investigator Name and Signature _____

Date: Place:

QUESTION:

If any enquiries in the future or in case of research related injury illness, you may contact following person.

Chairman, College ethical Dissertation and Research committee, J.N.Medical College, Belgaum.	Guide , Professor Department of General Medicine, J.N.Medical College, Belgaum.	Post-Graduate, Department of General Medicine, J.N.Medical College, Belgaum.

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Annexures

Annexure II

ANNEXURE II – PROFORMA

Name :	IP No.
Age / Sex	D.O.A
Address	D.O.D.
Income Per month	Level of Education
Profession / Occupation	Languages

UKPDS – Brain bank criteria for PD

NMS quest questionnaire

MMSE

Past History

Any other Neurological illness :

Hypertension :

Diabetes :

Cardiac Illness :

Any systemic illness :

Thyroid disorder:

Drug History

Family History

Personal History

Diet

Smoking

Alcohol

Tobacco

General Examination

B. P. - Supine

- Standing

Weight

Pulse rate Temperature

Peripheral pulses

RR

Carotid

Skin Pallor

Icterus Cyanosis

Clubbing Pedal edema

Lymph Nodes Bleeding diatheses

Deformities

Subcutaneous nodules

Neuro-cutaneous markers

Joints

CVS

RS

PA

Neurological examination : (handedness)

Mental functions

Consciousness

Orientation

Language

Visuspatial orientation

Praxis

Dressing

Behavioural abnormality – NPI

Memory - MMSE

Right left orientation

Insight

Judgment

Abstract thinking

Cranial nerves

Olfacotry – Sniffin battery test

Optic nerves

Oculomtor trochlear and Abducent nerve

Trigeminal nerve

Facial nerve

Glossopharyngeal nerve

Vagus nerve

Accessory nerve

Hypoglossal nerve

Motor system

Involuntary movements

Tone

Power

Cerebellar signs

Sensory system	Lateral Column and Posterior Column
Rombergism	
Cortical sensations	
Graphesthesia	
Muscle stretch reflexes	
Jaw jerk	
Release reflexes	
Superficial reflexes	
Gait	
Signs of meningeal irritation	
Provisional diagnosis	

NMS QUEST QUESTIONNAIRE

		Yes	**No**
1.	Dribbling of saliva during the daytime		
2.	Loss or change in your ability to taste or smell		
3.	Difficulty swallowing food or drink or problems with choking		
4.	Vomiting or feelings of sickness (nausea)		
5.	Constipation (< 3 bowel movements a week) or having to strain to pass a stool (faecea)		
6.	Bowel (fecal) incontinence		
7.	Feeling that your bowel emptying is incomplete after having been to the toilet		
8.	A sense of urgency to pass urine makes you rush to the toilet		
9.	Getting up regularly at night to pass urine		
10.	Unexplained pains (not due to known conditions such as arthritis)		
11.	Unexplained change in weight (not due to change in diet)		
12.	Problems remembering things that have happened recently or forgetting to do things		
13.	Loss of interest in what is happening around you or doing things		
14.	Seeing or hearing things that you know or are told are not there		
15.	Difficulty concentrating or staying focused		

		Yes	***No***
16.	Feeling sad, low, or blue		
17.	Feeling anxious, frightened or panicky		
18.	Feeling less interested in sex or more interested in sex		
19.	Finding it difficult to have sex when you try		
20.	Feeling light headed, dizzy or weak standing from sitting or lying		
21.	Falling		
22.	Finding it difficulty to stay awake during activities such as working, driving or eating		
23.	Difficulty getting to sleep at night or staying asleep at night		
24.	Intense, vivid dreams or frightening dreams		
25.	Talking or moving about in your sleep as if you are “acting” out a dream		
26.	Unpleasant sensations in your legs, at night or while resting, and a feeling that you need to move		
27.	Swelling of your legs		
28.	Excessive sweating		
29.	Double vision		
30.	Believing things are happening to you that other people say are not true		

Have you experienced any of the following in the last month?

All the information you supply through this form will be treated with confidence and will only be used for the purpose for which it has been collected. Information supplied will be used for monitoring purposes.

Non-movement problems in Parkinson's

The movement symptoms of Parkinson's are well known. However, other problems can sometimes occur as part of the condition or its treatment. It is important that the doctor knows about these, particularly if they are troublesome for you.

A range of problems is listed below. Please tick the box 'Yes' if you have experienced it during the past month. The doctor or nurse may ask you some questions to help decide. If you have not experienced the problem in the past month tick the 'No' box. You should answer 'No' even if you have had the problem in the past but not in the past month.

ANNEXURE III - MASTER CHART

Serial number	In/Out patient Number	Sex	Age (Years)	Education	Diagnosis	Duration of illness	Neurological examination																																					
							MMSE Score	Diagnosis of PD		NMS Quest Questions																																			
								UKPDS Criteria	H & Y Staging	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30
1	1431737	M	52	G	ND	3m	30	SF	2.50	N	Y	N	N	Y	N	Y	Y	N	Y	N	Y	N	N	Y	N	N	Y	Y	N	N	N	Y	N	N	Y	N	N	N	N
2	1666185	F	48	P	ND	1y	30	SF	1.00	N	N	N	Y	N	N	Y	N	N	Y	N	N	N	N	Y	Y	N	Y	Y	N	N	N	Y	Y	N	Y	N	Y	N	N
3	1426588	M	66	G	ON	1y	26	SF	2.00	N	Y	N	Y	Y	N	N	N	Y	Y	Y	Y	N	N	Y	Y	N	N	Y	Y	N	Y	N	Y	N	N	Y	Y	Y	N
4	1918023	F	55	IL	ND	1.5y	30	SF	2.00	N	Y	N	Y	Y	N	Y	N	Y	Y	Y	N	Y	N	Y	Y	N	N	N	Y	N	N	Y	N	N	N	Y	Y	N	N
5	1833176	M	64	P	ND	1y	30	SF	3.00	N	Y	Y	Y	Y	N	Y	Y	Y	Y	N	Y	Y	N	Y	Y	N	Y	Y	N	Y	N	Y	N	N	N	Y	Y	N	N
6	958757	M	65	S	OT	2.5y	30	SF	3.00	N	Y	Y	Y	Y	N	Y	N	Y	Y	N	Y	Y	N	Y	Y	Y	Y	Y	N	N	N	Y	N	N	Y	Y	N	N
7	1883888	M	67	P	ND	2y	23	SF	3.00	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	N	Y	N	N	Y	N	N	Y	Y	Y	N	Y	Y	N	N	Y	N	Y	N	N
8	1454978	M	64	S	OT	2y	30	SF	3.00	N	Y	N	Y	Y	N	Y	N	Y	Y	N	Y	Y	N	Y	Y	N	Y	N	Y	N	N	Y	N	N	Y	Y	Y	N	N
9	1910244	M	48	IL	OT	4y	30	SF	2.00	N	Y	Y	N	Y	N	Y	N	N	Y	Y	Y	Y	N	Y	N	N	Y	N	Y	N	Y	Y	Y	N	Y	N	Y	N	N
10	585898	M	60	G	OT	6y	27	SF	4.00	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	N	Y	Y	N	Y	Y	N	Y	Y	Y	N	Y	Y	Y	N	Y	N	N	N	N
11	154787	M	58	P	OT	10y	24	SF	2.50	N	Y	Y	N	Y	Y	N	N	N	Y	N	Y	Y	Y	Y	Y	N	Y	Y	N	N	N	Y	Y	N	Y	Y	N	N	Y
12	601406	M	46	PU	OT	6y	26	SF	3.00	N	N	N	Y	N	N	Y	N	N	Y	N	N	Y	N	N	Y	N	Y	Y	N	N	N	Y	Y	N	N	N	Y	N	Y
13	1203850	M	55	S	OT	2y	30	SF	3.00	N	Y	N	Y	Y	N	Y	N	Y	Y	N	Y	Y	N	Y	Y	N	Y	Y	Y	N	N	Y	Y	N	Y	Y	Y	N	N
14	2074764	F	45	PU	ND	1y	28	SF	3.00	N	Y	N	Y	N	N	Y	N	N	Y	N	Y	Y	N	N	Y	Y	Y	Y	N	N	N	Y	N	Y	Y	N	Y	N	N
15	2087254	F	45	S	ND	2y	24	SF	2.50	Y	N	N	Y	Y	N	Y	N	N	Y	N	N	N	N	Y	N	N	Y	Y	Y	N	N	Y	N	Y	N	N	Y	N	N
16	2024826	F	65	PU	ND	3m	28	SF	1.00	N	N	N	Y	Y	Y	N	Y	N	Y	Y	Y	N	N	Y	N	N	Y	Y	Y	N	Y	N	Y	N	Y	Y	Y	N	N
17	1342955	M	55	G	ND	1m	30	SF	2.00	N	N	N	Y	Y	N	N	Y	N	N	N	Y	N	N	Y	N	N	Y	Y	N	N	Y	N	N	N	N	N	N	N	N
18	1578995	F	48	S	ND	6m	30	SF	2.00	N	Y	N	Y	N	Y	Y	N	N	Y	N	N	Y	N	Y	N	Y	Y	Y	N	N	Y	Y	N	N	Y	N	N	N	N
19	1650669	M	79	IL	ND	6m	29	SF	3.00	N	N	Y	Y	Y	Y	Y	N	Y	N	N	Y	Y	N	N	Y	Y	Y	Y	N	N	N	Y	N	N	Y	N	N	N	N
20	1449055	M	72	S	ND	5m	24	SF	4.00	Y	Y	Y	Y	Y	Y	N	Y	N	Y	N	Y	Y	N	N	Y	Y	Y	Y	Y	N	N	N	Y	Y	N	N	N	Y	N	N
21	1950624	M	62	IL	ND	2y	27	SF	3.00	Y	Y	N	Y	N	Y	N	Y	N	Y	N	Y	Y	N	Y	Y	N	N	Y	Y	Y	Y	N	Y	N	N	Y	N	Y	N	N
22	1858950	M	58	G	ND	3y	26	SF	3.00	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	N	Y	N	N	Y	Y	N	Y	N	Y	N	Y	N	N	Y	Y	N	N	N	N
23	1778568	M	60	G	ND	6m	30	SF	2.00	N	N	N	N	Y	N	N	Y	Y	N	N	Y	N	N	Y	Y	N	Y	N	Y	N	N	Y	N	N	N	N	Y	N	N
24	2086517	F	50	P	ND	10m	30	SF	1.00	N	Y	N	N	N	N	Y	N	Y	Y	N	N	Y	N	N	N	Y	N	Y	N	N	N	Y	Y	N	Y	N	N	N	Y
25	1292724	F	44	C	ND	3m	30	SF	1.00	N	Y	N	N	N	N	Y	N	N	Y	Y	N	N	N	N	Y	Y	Y	Y	N	N	N	Y	N	N	N	N	N	N	N
26	1739940	M	65	IL	ND	3m	27	SF	2.00	N	N	N	N	Y	N	N	Y	Y	Y	N	Y	Y	N	Y	N	N	N	Y	N	N	N	Y	N	N	Y	N	N	N	N
27	1775166	F	50	P	ND	6m	25	SF	2.00	N	N	N	N	N	N	Y	N	N	N	N	N	N	N	Y	N	N	Y	Y	Y	Y	N	Y	N	N	Y	N	N	N	N
28	1162166	F	52	S	OT	2y	26	SF	2.50	N	N	N	Y	N	N	Y	N	N	Y	Y	Y	Y	N	N	Y	N	Y	Y	Y	N	N	Y	N	N	Y	N	N	N	N
29	1591001	M	76	IL	ND	2y	28	SF	3.00	N	Y	N	Y	Y	N	N	Y	Y	N	N	N	N	N	N	N	N	N	N	Y	N	N	Y	N	N	Y	N	Y	N	N

ANNEXURE III - MASTER CHART

Serial number	In/Out patient Number	Sex	Age (Years)	Education	Diagnosis	Duration of illness	Neurological examination																																					
							MMSE Score	Diagnosis of PD		NMS Quest Questions																																			
								UKPDS Criteria	H & Y Staging	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30
30	614693	F	68	IL	OT	5y	18	SF	3.00	Y	Y	N	Y	Y	N	N	N	Y	Y	N	Y	Y	Y	N	Y	Y	N	N	Y	N	N	Y	Y	N	Y	N	N	N	Y
31	795875	F	65	P	OT	6y	24	SF	3.00	N	Y	N	Y	Y	N	Y	N	Y	Y	N	N	N	N	N	N	Y	N	N	Y	Y	N	Y	Y	N	N	Y	Y	N	N
32	1203850	M	59	S	OT	3y	23	SF	2.50	N	N	Y	N	Y	N	N	Y	Y	N	N	Y	Y	N	Y	N	N	Y	Y	Y	Y	N	Y	N	N	N	Y	N	N	Y
33	1666638	F	66	G	OT	6m	30	SF	1.00	N	Y	N	N	N	N	Y	N	Y	Y	Y	N	N	N	N	Y	N	N	N	Y	Y	N	Y	N	N	Y	Y	N	N	N
34	1628269	F	45	C	ND	3m	29	SF	1.00	N	N	N	N	N	N	N	N	N	Y	N	N	Y	N	N	Y	Y	N	N	N	N	N	Y	N	N	N	N	N	N	N
35	1788292	F	68	P	OT	5y	24	SF	4.00	Y	Y	N	Y	Y	N	Y	N	Y	Y	N	N	Y	N	N	Y	Y	N	N	Y	N	N	N	Y	Y	Y	N	Y	N	N
36	1772568	M	60	SC	ND	1y	26	SF	1.50	N	N	N	N	N	N	Y	N	Y	N	N	Y	N	N	Y	N	N	N	N	N	N	Y	N	N	Y	N	N	N	N
37	1578995	F	48	G	ND	6m	30	SF	2.00	N	Y	N	N	N	N	Y	N	Y	Y	N	Y	N	N	N	N	Y	N	Y	Y	N	N	N	Y	N	N	N	Y	N	N
38	1454978	M	64	P	OT	2y	28	SF	1.50	Y	N	N	Y	N	Y	Y	Y	N	N	N	N	Y	N	N	Y	N	N	Y	Y	N	N	Y	N	N	Y	Y	N	N	N
39	1292724	F	44	C	OT	2y	30	SF	1.00	N	N	N	N	N	N	Y	N	N	Y	N	Y	N	N	N	N	N	Y	N	Y	N	N	Y	N	N	N	N	N	N	N
40	1203850	M	58	S	OT	4.5y	26	SF	4.00	N	Y	N	Y	Y	N	Y	N	Y	Y	N	Y	Y	N	Y	Y	N	N	Y	Y	N	N	Y	N	Y	Y	Y	N	N	Y
41	1531788	M	64	P	ND	1y	30	SF	3.00	N	Y	Y	Y	Y	N	Y	Y	Y	Y	N	Y	Y	N	Y	Y	N	Y	Y	N	Y	N	Y	N	N	N	Y	Y	N	N
42	796081	F	65	P	OT	6y	24	SF	3.00	N	Y	N	Y	Y	N	Y	N	Y	Y	N	N	N	N	N	N	Y	N	N	Y	Y	N	Y	Y	N	N	Y	Y	N	N
43	1203150	F	48	P	ND	1y	30	SF	1.00	N	N	N	Y	N	N	Y	N	N	Y	N	N	N	N	Y	Y	N	Y	Y	N	N	N	Y	Y	N	Y	N	Y	N	N
44	152850	F	50	C	ND	10m	30	SF	1.00	N	Y	N	N	N	N	Y	N	Y	Y	N	N	Y	N	N	N	Y	N	Y	N	N	N	Y	Y	N	Y	N	N	N	Y
45	1562811	M	59	S	OT	3y	23	SF	2.50	N	N	Y	N	Y	N	N	Y	Y	N	N	Y	Y	N	Y	N	N	Y	Y	Y	Y	N	Y	N	N	N	Y	N	N	Y
46	1820133	M	72	S	ND	5m	24	SF	4.00	Y	Y	Y	Y	Y	Y	N	Y	N	Y	N	Y	Y	N	N	Y	N	N	Y	Y	Y	Y	N	N	N	Y	Y	N	N	N
47	1712611	F	48	S	ND	6m	30	SF	2.00	N	Y	N	Y	N	Y	Y	N	N	Y	N	N	Y	N	Y	N	Y	Y	Y	N	N	Y	Y	N	N	Y	N	N	N	N
48	1821566	M	55	IL	ND	1.5y	30	SF	2.00	N	Y	N	Y	Y	N	Y	N	Y	Y	Y	N	Y	N	Y	Y	N	N	N	Y	N	N	Y	N	N	N	Y	Y	N	N
49	1628159	F	52	S	OT	2y	26	SF	2.50	N	N	N	Y	N	N	Y	N	N	Y	Y	Y	Y	N	N	Y	N	Y	Y	Y	N	N	Y	N	N	Y	N	N	N	N
50	1602501	M	64	P	ND	1y	30	SF	3.00	N	Y	Y	Y	Y	N	Y	Y	Y	Y	N	Y	Y	N	Y	Y	N	Y	Y	N	Y	N	Y	N	N	N	Y	Y	N	N

Annexures

Annexure III

ANNEXURE III – KEY TO MASTER CHART

F	-	Female
G	-	Graduate
H&Y	-	Hoehn and Yahr staging
IL	-	Illiterate
M	-	Male
m	-	Months
MMSE	-	Minimental status examination
N	-	No
ND	-	Newly diagnosed
NMS	-	Non motor symptoms
OT	-	On treatment
P	-	Primary
PD	-	Parkinson’s disease
PU	-	Pre-University
S	-	Secondary
SF	-	Satisfied
UKPDS	-	United Kingdom Parkinson Disease Society
y	-	years
Y	-	Yes