PARKINSON'S DISEASE - A REVIEW

Olaitan C. Okunoye, Bolaji Otike-Odibi
Department of Medicine, University of Port Harcourt Teaching Hospital.
Port Harcourt, Nigeria.

Correspondence:
Dr O. C Okunoye
University of Port Harcourt Teaching Hospital. Port Harcourt, Nigeria. olaitanok@gmail.com

SUMMARY
Parkinson's disease (PD) is one of the most common neurodegenerative diseases of insidious onset in middle or late age. It is characterized by slowly progressive akinesia, rigidity, tremor and postural instability.[1] It occurs in all ethnic groups. PD affects both sexes and becomes increasingly common with advancing age.[2]
PD is probably a result of multiple factors acting together, including ageing, genetic susceptibility, and environmental exposures.[3]
PD affects many aspects of patients' life outside the characteristic motor features, which are the main focus of routine treatment by many clinicians. Non-motor features such as depression, psychosis and cognitive impairment also occur.

INTRODUCTION

More than 180 years ago, James Parkinson first described the disorder that bears his name, and 30 years ago levodopa, still the most effective therapy, was introduced.[1] Parkinson's disease (PD) is one of the most common neurodegenerative diseases of insidious onset in middle or late age. It is characterized by slowly progressive akinesia, rigidity, tremor and postural instability.[2] It occurs in all ethnic groups. PD affects both sexes and becomes increasingly common with advancing age.[3] Age is the single most consistent risk factor, and with the increasing age of the general population, the prevalence of PD will rise steadily in the future.1 Estimates of the prevalence of PD vary considerably, from 31-328 per 100,000 persons worldwide.[4-7] In Nigeria, the crude prevalence is 59 cases per 100,000.[8]

PD has a wide range of impact on the patients' physical, emotional, psychological and socioeconomic functioning. The impact of this disease is indicated by the fact that mortality is two to five times as high among affected persons as among age-matched controls,[9-11] resulting in a marked reduction in life expectancy.[10] Infact, neurodegenerative diseases (PD, motor neuron disease, and dementia) are projected to surpass cancer as the second most common cause of death among the elderly by the year 2040.[12] Thus, Parkinson's disease greatly shortens life as well as causing debility resulting in poor quality of life.

PD affects many aspects of patients' life outside the characteristic motor features, which are the main focus of routine treatment by many clinicians. Non-motor features particularly the psychosocial manifestations such as depression, psychosis and cognitive impairment, which can be more disabling than the motor symptoms themselves, are ignored. Patients with PD also suffer restrictions in mobility, falls, emotional disorders, social embarrassment, isolation, sleep disturbances, dyskinesias and fluctuations.[13]

EPIDEMIOLOGY AND CLINICAL FEATURES

Historical Background

In his 1817 "An essay on the shaking palsy", James Parkinson first described the clinical syndrome that was later to bear his name.[14]
He identified six cases, three of whom he personally examined; three he observed on the streets of London. Previously referred to as "paralysis agitans", Charcot later in 19th century gave credit to Parkinson by referring to the disease as "maladie de Parkinson" or Parkinson's disease (PD). Charcot also recognized non-tremulous forms of PD and correctly pointed out that slowness of movement should be distinguished from weakness or

"lessened muscular power", a term originally used by Parkinson.[15] More than 100 years passed (1919) after the original description by Parkinson before it was recognized that patients with PD lose cells in the substantia nigra, and 140 years passed (1957) before dopamine was discovered as a putative neurotransmitter by Carlsson and colleagues in Lund, Sweden.[16]

The discovery by Ehringer and Hornykiewicz in 1960[16,17] that dopamine concentrations are markedly decreased in the striatum of patients with PD paved the way for the first trials of levodopa in the following year[18] and subsequent award of the Nobel Prize in Medicine to Carlsson in 2000.[19] The ability of injected levodopa to improve akinesia in patients with PD was first demonstrated in 1961 and was followed by the development of oral levodopa later in the decade.[18,20]

More recently genetic mutations, abnormal handling of misfolded proteins by the ubiquitin/proteasome and the autophagy-lysosomal systems, increased oxidative stress, mitochondrial dysfunction, inflammation and other pathogenic mechanisms have been identified as contributing factors in the death of dopaminergic and non-dopaminergic cells in the brain of patients with PD.[21,22]

Epidemiology

Parkinson's disease (PD) occurs throughout the world, in all ethnic groups, and affects both sexes roughly equally or with only a slight predominance among males.[23] The prevalence of PD varies considerably with estimates ranging from 31-328 per 100,000 persons worldwide.[4-7] This increases exponentially with age between 65 and 90 years; approximately 0.3 percent of the general population and 3 percent of people over the age of 65 have PD.[24] Five to 10 percent of patients have symptoms before the age of 40 years (this variety of the disorder is classified as "young onset Parkinson's disease").[1] The lowest reported incidence is among Asians and African blacks, whereas the highest is among whites.[1] This could be due to the marked apparent geographic variation that has been reported.[25]

In a systematic review of epidemiologic and genetic studies of PD in Africa, Okubadejo et al[26] found that the studies suggested some intra-continental geographic variations in PD prevalence but overall, the prevalence figures and the incidence rates of PD in Africa appeared lower than those reported for European and North American populations.

Generally, PD is said to be less common in Africa than elsewhere in the world though previous studies have been based on small numbers. Also, these differences may be due to the diagnostic criteria used, case finding methods and population. Developing countries like Nigeria have very few facilities for chronic disease management and non-communicable diseases which though on the increase, tend to play second fiddle to infectious diseases like malaria and HIV/AIDS.[27,28]

In a door-to-door study performed in a rural area of Nigeria in 1986 by Osuntokun et al, a crude prevalence of 59 per 100,000 persons was reported.[8] This appears to be the only prevalence study so far in Nigeria.

Though African blacks have much lower incidence than American blacks; the prevalence of Lewy bodies in the brains of Nigerians is similar to that in Western population.[29] This pattern suggests that the propensity for development of PD is universal but that local environmental factors may have a role in causing the disorder.

Aetiology and risk factors

Parkinsonian symptoms can arise from either neuropathologic condition of Parkinson's disease (idiopathic Parkinson's disease) or other forms of parkinsonism. For neuropathologic Parkinson's disease (PD), about 90% of cases are sporadic, with no clear etiology; an additional 10% have a genetic origin, and at least 11 different linkages with 6 gene mutations have been identified.[30,31,32] Despite the overall rarity of the familial forms, the identification of these several genetic variations has been associated with PD in different populations. This is not so for sub-Saharan Africa. Okubadejo et al[33] screened a cohort of PD patients (n= 57) and healthy controls (n=51) from Nigeria for mutations in the genes PRKN, LRRK2 and ATXN3.No pathogenic mutations were found in any of the genes. This could be due to the small sample size as very large samples are needed to identify genes. It is also possible that these mutations in Caucasians are not important here. There may be a need to search for other genes in Nigerians. However a combination of environmental factors or toxins, genetic susceptibility, and the aging process may account for many sporadic cases.[30,31,34,35]

The underlying pathological findings in PD are injury to the doperminergic projections from the substantia nigra pars compacta to the caudate nucleus and putamen (striatum). Intraneural Lewy bodies and Lewy neuritis are the pathologic hallmarks of the disease. Clinical signs of PD are evident when about 80% of striatal dopamine

and 50% of nigral neurons are lost.[36] Lewy bodies are not confined to the substantia nigra and can be seen in cortex, amygdala, locus ceruleus, vagal nucleus, and the peripheral autonomic nervous system.[37] Lewy bodies and neurites in these non-motor areas could account for many of the non-motor symptoms.

Setting aside the few individuals with PD who have a known gene mutation or exposure to 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine (MPTP), the cause of this disorder is unknown. PD is probably a result of multiple factors acting together, including ageing, genetic susceptibility, and environmental exposures.[3]

Ageing

Pathologically, ageing is associated with a decline of pigmented neurons in the substantia nigra pars compacta. Incidental Lewy bodies are reported in up to 16% of the elderly asymptomatic people at autopsy.[38] In a SPECT study,[39] an age-related decline in striatal dopamine transporters was reported, but no difference was noted between the caudate and putamen, a pattern that differs from that seen in PD. Although the incidence of PD increases with age, this is generally accepted not to be simply an acceleration of ageing.

Genetic Predisposition

Most people with PD do not have a family history. About 15% of patients have a first-degree relative with the disease; typically without a clear mode of inheritance.[40] Some genetic loci associated with autosomal dominant or recessive parkinsonism have been identified. However, general environmental exposures can also account for familial patterns.[34]

Findings of most twin study do not show enhanced concordance in monozygotic twins. Results of a twin study showed little concordance in twins when PD develops after age 50 years, but complete concordance in monozygotic twins for disease onset before this age.[41] This finding suggests that genetic susceptibility plays a more significant part in early-onset than in late-onset disease.[34] The discovery of various genes and gene loci in familial PD has greatly enhanced interest in genetic contribution to this disorder. This has also expanded our understanding of the potential mechanisms in neurodegeneration in both familial and sporadic PD.[34]

Alpha-Synuclein (PARK 1) This gene is linked to familial disease and is said to code for the alpha synuclein protein. PARK 1 involves mutations in the alpha-synuclein gene(A50T and A30P).[42,43] In addition, multiplications of the wild-type alpha-synuclein gene have been identified in large autosomal dominant kindred with PD and tremor and duplication in one of 42 familial probands with early-onset PD[44,45] A third alpha-synuclein point mutation (E46K) has been reported in an autosomal dominant family with parkinsonism and Lewy body dementia.[46] The exact function of the alpha-synuclein protein-so named because it seemed to localize to synaptic terminals and nuclei-is unknown, but it is a major component of Lewy bodies.[47] Lewy bodies are intracytoplasmic aggregates comprising several proteins, including ubiquitin and alpha-synuclein, and have supported the notion that abnormal protein handling might be important in PD pathogenesis.[48]

PARKIN (PARK 2). PARK2 gene mutations were first linked to an autosomal recessive juvenile-onset form of PD (ARJPD) [49]. In 1998, the gene responsible for ARJPD was discovered and mapped to 6q25.2-q27[50]. Several different parkin mutations cause autosomal recessive disease,[51] and these could account for up to half of early-onset cases of the disorder and perhaps even a higher proportion of juvenile-onset PD.[52] Pathological findings in young-onset PD with the parkin mutation show cell loss in substantia nigra pars compacta and the locus coeruleus but, typically without Lewy bodies.[34] PARK 2 encodes parkin, which functions as an E3 ligase, ubiquitinating proteins for destruction by the proteosome[53,54]. The discovery that parkin is an ubiquitin-protein ligase,[53] and that alpha synuclein is ubiquitinated by parkin,[55] lends support to the hypothesis that failure of the ubiquitin-proteasome system is the common denominator in the pathogenesis of PD.

UCH-L 1(PARK 5). The discovery of PD in association with a mutation in the gene encoding ubiquitin carboxylase L1 futher supports the relevance of the ubiquitin/proteasomal system (UPS) in PD pathogenesis.[56] UCH-L1 is an enzyme that hydrolyzes the C-terminus of ubiquitin to generate ubiquitin monomers that can be recycled to clear other proteins.

PINK1 (PARK 6) Mutations in PINK1 (PTEN [phosphatase and tensin homolog deleted on chromosome ten]-induced kinase 1) were found to be responsible for familial recessive form of early-onset parkinsonism, previously mapped to chromosome 1p36.[57] The PINK1 gene is ubiquitously transcribed and is believed to encode a mitochondrial kinase.[57] PINK1 is located in the mitochondria. Preliminary data have suggested that PINK1 may play a role in protecting cells

against stress conditions that affect mitochondrial membrane potential, but the downstream targets through which PINK1 mediates its protection have not been identified.[48]

PARK 7 is located close to the region for PARK6 on chromosome 1p36, but no overlaps exist between markers for these two genes. PARK7 is linked to an autosomal recessive early-onset form of PD.[58] This gene codes for the DJ1 protein, which might be implicated in the response to oxidative stress.[34]

LRRK2 (PARK 8). Mutations in the LRRK2 gene are of particular interest because they appear to be the most common mutations thus far identified in either familial or sporadic PD. The LRRK2 G2019S mutation alone has been reported in 2.8% to 6.6% of autosomal dominant PD families[59,60] and in 2% to 8% of sporadic cases[61,62.] The G2019S mutation has variable penetrance. Although other LRRK2 mutations are described, the G2019S mutation remains the most common mutation in patients with either sporadic or familial PD. This mutation has not been seen in Alzheimer's disease or in parkinsonian syndromes other than idiopathic PD.[63,64] The LRRK2 gene encodes a 286-kDa cytoplasmic protein that is widely expressed in the brain.[65] It appears to have multiple functions. These includes its involvement in cytoskeletal responses to external stimuli, vesicular trafficking, and the stimulation of stress-activated kinase.[66]

Environmental exposure

Several studies have sought to define the environmental contribution to the aetiology of PD. A rural residency appears to increase the risk for PD and, in particular, young-onset PD.[67,68] However, this finding has not been confirmed in all studies.[69] Rural living is associated with farming and pesticide use, and an association with agricultural industry has been found with increased incidence in PD patients.[70] In addition, a further lifestyle study showed increased herbicide exposure in patients with PD.[71] Organochloride pesticides[69,72] and dithiocarbamates have been identified as risk factors for PD,[69,70] and have also been shown to enhance MPTP toxicity.[73] 1-Methyl 4-phenyl 1,2,3,6 tetrahydropyridine(MPTP), a meperidine analogue designer drug, is known to produce parkinsonism in humans, other primates, and rodents through uptake and conversion mechanisms that target the nigrostriatal pathway.[74] Other agents include-Pyrethroid pesticides, Rotenone, Paraquat and Manganese. It is noteworthy that these agents result in inhibition of mitochondrial NADH CoQ reductase (complex 1) and are free radical generators, features of direct relevance to PD.

Another rural factor that has been linked to PD is the consumption of well water,75 although this may simply be further evidence in support of herbicides or pesticides as aetiologic factors of PD.

Two environmental factors have been reported to lower the risk for PD: cigarette smoking76 and coffee drinking.77 The mechanisms through which they reduce risk are not known.

Infection has also been suggested to be a risk factor for the development of PD as a subset of affected individuals developed post-encephalitic parkinsonism. More recent analysis with RNA detection methods on autopsy material has disputed this association.[78]

A number of studies have also evaluated diet in patients with PD, in an attempt to assess the possible role of inadequate intake of antioxidants, which might have predisposed patients to insult from other exogenous and endogenous sources. In general, these studies have been inconclusive.[1]

CLINICAL ASSESSMENT

PD is diagnosed based on clinical criteria; there is no definite test for diagnosis. Historically, pathological confirmation of the hallmark Lewy body on autopsy has been considered the criterion standard for diagnosis.[79] In clinical practice, diagnosis is typically based on the presence of a combination of cardinal motor features, associated and exclusionary symptoms, and response to levodopa.[80] However, clinical diagnosis of this disorder has become more rigorous, with gradations of diagnostic certainty, including possible, clinically probable, and clinically definite PD as summarized below.

Diagnostic criteria have been developed by the UK Parkinson's Disease Society Brain Bank[81,82] (which was employed in this study and discussed in chapter three) and the National Institute of Neurological Disorders and Stroke (NINDS).[83]

Below is a summarized version of diagnostic criteria.

TABLE 1: SUMMARY OF DIAGNOSTIC CRITERIA FOR PARKINSON'S DISEASE

Clinical diagnostic criteria for PD[84,85]
CLINICALLY POSSIBLE
One of:
Asymmetric resting tremor
Asymmetric rigidity
Asymmetric bradykinesia
CLINICALLY PROBABLE
Any 2 of:
Asymmetric resting tremor
Asymmetric rigidity
Asymmetric bradykinesia
CLINICALLY DEFINITE
The criteria for clinically probable and a definitive response to anti-Parkinson drugs
EXCLUSION CRITERIA
Exposure to drugs that can cause parkinsonism such as neuroleptics, some antiemetic drugs, tetrabenazine,and reserpine, flunarizine, and cinnarizine
Cerebellar or corticospinal tract signs
Severe dysautonomia
History of encephalitis or recurrent head injury
Severe subcortical white-matter disease, hydrocephalus, or other structural lesions revealed by magnetic resonance imaging scan.

Clinical grading scales

A number of rating scales are used for the evaluation of motor impairment and disability in patients with PD.

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).[88,86]

The **Unified Parkinson's Disease Rating Scale (UPDRS)** is the most well established scale for assessing disability and impairment.[87,88] It is a rating tool used to follow the longitudinal course of PD. It is made up of the- 1) Mentation, Behaviour, and Mood, 2) Activities of Daily Living (ADL), and 3) Motor sections. These are evaluated by interview. A total of 199 points are possible.199 represents the worst (total disability), while 0—no disability. For the motor examination, a total of 108 is possible.

CLINICAL FEATURES

There are four cardinal features of PD that can be grouped under the acronym TRAP: Tremor at rest, Rigidity, Akinesia (or bradykinesia) and Postural instability. However two cohorts of PD patients exist- those with tremors and those with postural instability as primary manifestation.

The rate of deterioration is variable in both forms of PD but worse and more rapid in patients with the postural instability gait difficulty (PIGD) form.[91,92,89,90]Also patients who are older and have the PIGD form of PD at onset experience more rapid disease progression than those who are younger at onset and have the tremor dominant form of PD.

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.[19]

Bradykinesia -This refers to slowness of movement and is the most characteristic clinical feature of PD occurring in about 80%-90% of patients.[91,92]

Bradykinesia is a hallmark of basal ganglia disorders, and encompasses difficulties with planning, initiating and executing movement and with performing sequential and simultaneous tasks.[93] The initial manifestation is often slowness in performing activities of daily living and slow movement and reaction times.[94,95] This may include difficulties with tasks requiring fine motor control (eg, buttoning, using utensils). Other manifestations of bradykinesia include loss of spontaneous movements and gesturing, drooling because of impaired swallowing, [96] monotonic and hypophonic dysathria, loss of facial expression (hypomimia) and decreased blinking, and reduced arm swing while walking.

Tremor -Rest tremor which occurs in 70%-90%[91,92] of patients is the most common and easily recognized 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 the an extremity. Hand tremors are described as supination-pronation ("pill rolling") tremors that spread from one hand to the other.[19]

Rigidity -More than 90% of patients with Parkinson's disease have rigidity. This is characterized 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).[97,98]

Postural instability -This is due to loss of postural reflexes and is generally a manifestation of the late stages of PD and usually occurs after the onset of other clinical features. It reflects progression to advanced stages of PD and predisposes to falls and injuries[97,98]

Other motor symptoms include - Shuffling gait characterized by short steps, with feet barely leaving the ground, producing an audible shuffling noise.

Stooped, forward-flexed posture is seen in patients with PD.In severe forms, the head and upper shoulders may be bent at a right angle relative to the trunk (camptocormia).[99]

Gait freezing is a manifestation of akinesia (an inability to move), which is characterized by an inability to move the feet. This may worsen in tight, cluttered spaces or when attempting to initiate gait.

NON-MOTOR FEATURES OF PARKINSON'S DISEASE

The clinical course of Parkinson's disease (PD) is not limited to motor symptoms. A variety of non-motor symptoms occur and are a common and underappreciated feature of PD. Akinyemi et al reported the occurrence of non-motor symptoms in

Nigerians with PD.[100] They include depression, cognitive/neurobehavioral disorders, and autonomic dysfunction, sensory and sleep abnormalities.

Increasingly, it is recognized that non-motor symptoms, especially depression, dementia, and psychosis, contribute to excess disability in PD.[101,102,103] Non-motor symptoms dominate the clinical picture as PD progresses and may also contribute to quality of life and shorten life expectancy.[102,104] Most do not respond to, and may be exacerbated by, dopamine replacement therapy.[102] Of concern is that, in contrast to motor symptoms, non-motor symptoms of PD are frequently unrecognized and either untreated or poorly treated in clinical practice leading to increased healthcare costs and utilization.[102]

Depression is frequent in PD and the most common neurobehavioral disorder, affecting up to 50% of patients which is several times the prevalence in the general population.[92,102,104,105,] Depression commonly co-exists with anxiety and can occur at any time in the course of the disease, including before onset of motor symptoms.[106] The impact of depression in PD patients ranges from mild manifested as an unwillingness to cooperate, to marked manifested as a complete withdrawal and social isolation.[106]

Cognitive impairment does occur in PD despite the original description as a disorder in which "the senses and intellect remain uninjured".[14] It is an important determinant of quality of life, care giver burden and mortality.[107,] Akinyemi et al[108] studied 51 Nigerians with PD and compared with 50 demographically matched controls using the modified Community Screening Instrument for Dementia (CSI'D) showed that 21.6% of the patients with PD exhibited cognitive impairment. Cognitive dysfunction encompassed memory, language, and executive dysfunction.

Autonomic dysfunction is well recognized in PD, particularly as the disease progresses. It may be the presenting feature of PD. Features include orthostatic hypotension, sweating dysfunction and erectile dysfunction.[109] Okubadejo et al[109]studied the frequency of autonomic dysfunction in 33 patients with PD in Nigeria and age-matched controls. The autonomic function tests utilized were heart rate variability to deep breathing, standing and the valsalva manoeuvre and blood pressure response to standing. They found that autonomic dysfunction was common in Africans with PD, especially those over the age of 65years.

Sleep disorders – Although sleep disturbances (e.g. excessive sleepiness, sleep attacks, insomnia and day time somnolence) were once attributed to the pharmacological therapy for PD,[119,110] some clinicians now believe that these features are an integral part of the disease. Collective prevalence of sleep disorders is estimated between 60% and 90% at some time over the course of the disease.[97.98,105] The sleep abnormalities observed in patients with PD may possibly be related to 50% loss of hypocretin (orexin) neurons.[111,112]

Sensory abnormalities such as olfactory dysfunction, pain, paraesthesia, akathasia and oral pain are frequent but are often not recognized as parkinsonian. Olfactory dysfunction seen in 70%-100% of patients occurs early in the disease and may be a preclinical marker of motor symptoms.[97,98,105] It has been postulated that olfactory dysfunction is related either to neuronal loss in corticomedial amygdala or to decreased doperminergic neurons in the olfactory lobe.[113]

Parkinson's disease (PD) also has substantial implication for patients' social life. Problems with monotonous speech or fixed facial expression can be embarrassing and potentially ostracizing features. Leisure activities which involve going out or those which rely on physical dexterity can become difficult to maintain which can lead to social isolation. Feelings of shame or stigma can result when a lack of social competence is perceived.[114] All these result in a poor quality of life in PD patients.

PARKINSONISM AND DIFFERENTIAL DIAGNOSIS

Parkinsonism describes a syndrome characterized by rigidity, tremor, and bradykinesia, of which Parkinson's disease is the main cause. Parkinsonian disorders can be classified as: primary (idiopathic) parkinsonism, secondary (acquired or symptomatic) parkinsonism, heredodegenerative parkinsonism and multiple system degeneration (parkinsonism plus syndromes). Several features, such as tremor, early gait abnormality (e.g, freezing), postural instability, pyramidal tract findings and response to levodopa, can be used to differentiate PD from other parkinsonian disorders.

Familial PD and familial parkinsonism are terms used to describe disease entities with either an autosomal

dominant (with variable penetrance) or autosomal recessive pattern. Parkinson-plus syndromes refer to diseases that include parkisonism combined with other clinical signs. These include dementia with Lewy bodies, multiple system atrophy, progressive supranuclear palsy, and corticobasal degeneration.[34]

The differential diagnosis of this disorder includes normal ageing, essential tremor, drug-induced parkinsonism, the Parkinson-plus syndromes, vascular parkinsonism, and normal pressure hydrocephalus.[34] Less common entities with parkinsonism include dopa-responsive dystonia,[114] juvenile-onset Huntington's disease,[115] and pallidopontonigral degeneration.[116]

Essential tremor

Essential tremor is characterized by action tremor that typically interferes with drinking from a cup rather than resting tremor.[117] It tends to be bilateral but frequently asymmetric, and in half of patients there is a family history. The frequency of essential tremor is higher (8 Hz) than that of PD, but it falls with age. In severe cases, essential tremor can be present at rest, making its differentiation from parkinsonian tremor difficult. The presence of rigidity, bradykinesia, and response to dopaminergic treatment help differentiate PD from essential tremor.

Drug-induced Parkinsonism

Drug-induced parkinsonism usually arises after exposure to neuroleptics.[118] Antiemetic and promotility agents (promethazine, prochlorperazine, and metoclopramide), reserpine, tetrabenazine, and some calcium-channel blockers (flunarizine and cinnarizine) can also cause parkinsonism. Symptoms are symmetric, and drug-induced parkinsonism resolves when the drug is stopped, although resolution can take weeks to months.

Progressive supranuclear palsy

In progressive supranuclear palsy, oculomotor disturbance, speech and swallowing difficulties, imbalance with falls, and frontal dementia are predorminant.[119] Patients have symmetric onset of parkinsonism, early postural instability, severe axial rigidity, absence of tremor, and a poor response to dopaminergic treatment. Supranuclear gaze palsy, especially of downward gaze, is the defining characteristic. Blepharospasm and eyelid opening apraxia are also typical.

Multiple system atrophy

Multiple system atrophy (MSA) is the current term for grouping the previously separate entities olivopontocerebellar atrophy, Shy-Drager syndrome, and striatonigral degeneration.[120] It presents with parkinsonism, cerebellar, autonomic (orthostatic hypotension, bladder and bowel dysfunction, temperature dysregulation), and pyramidal dysfunctions in various combinations. MSA-P (formerly striatonigral degeneration) is characterized by symmetric parkinsonism without tremor and early, pronounced postural instability. MSA-C (formerly olivopontocerebellar atrophy) manifests with cerebellar signs and parkinsonism. Corticospinal tract signs and respiratory stridor can be recorded in all categories of MSA. A poor response to dopaminergic treatment is seen.

Vascular parkinsonism and normal pressure hydrocephalus.

Vascular parkinsonism is attributable to multiple infarcts in the basal ganglia and the subcortical white matter.[121] Gait difficulty is a typical presentation. A wide-based shuffling gait is very suggestive of this entity. Tremor is usually absent. Brain imaging shows extensive small vessel disease. Dementia, pseudobulbar affect, urinary symptoms, and pyramidal signs frequently accompany vascular parkinsonism. No therapeutic response is seen to dopaminergic treatment. Normal pressure hydrocephalus can produce similar picture.[122]

HEALTH-RELATED QUALITY OF LIFE IN PARKINSON'S DISEASE

"Health-related quality of life" (HRQOL) is considered complementary to that of "duration (or quantity) of life". People want to live longer, but they also want to live better. HRQOL is a concept that is evolving in PD and other chronic diseases.

There are many sources of HRQOL decrease in PD. These include: gait disorder and slowness, freezing, falls, troubles in manual ability for activities such as feeding, dressing and bathing, constipation, drooling, dysphagia, depression, social embarrassment, communication problems, sleep disorders, fatigue, painful spasms, withdrawal, isolation and loneliness, loss of hobbies and

leisure activities, driving inability, severe dyskinesias, hallucinations and delirium related to therapy with dopaminergic drugs, and loss of employment in case of active patients.[8,123]

Many aspects of these disorders go unnoticed in clinical evaluation, and only HRQOL assessment allows them to be rated. Generic instruments have been used in a few studies measuring HRQOL in PD patients though not in our environment. Recently, specific instruments as PDQ-39 and PDQL-37 been designed and validated for QOL measurement in PD.

PHARMACOLOGIC TREATMENT

Protective treatment

None of the currently available treatments have been found to slow the progression of PD.

Selective monoamine oxidase B (MAO-B) inhibitor selegiline was initially thought to delay the onset of disability by slowing the progression of the disease, it is now thought that much of the effects were not sustained and selegiline did not delay the development of dyskinesias or fluctuations seen in response to Levodopa.[1]

High doses of the antioxidant vitamin E have also been proved to be ineffective in slowing the progression of the disease.

Medical treatment [124,125]

Treatment is aimed at correcting dopamine insufficiency and tailored to individual needs.

Current treatment involves symptomatic relief without effect on slowing disease progression. In, progressive disease, long term treatment requires follow up, dose adjustments and drug manipulation.

The choice of drug will depend on evidence of efficacy, side effects, cost, individual needs. This is tailored to disease severity at presentation.

Drug treatment options should be discussed with the patient/family. Adequate time interval should be allowed to assess responsiveness and dose escalation to reasonable dose before dismissing.

Cost and availability/access to drugs are also paramount in treatment of patients with PD.

Typically begin treatment in early PD with **EITHER** levodopa or a dopamine agonist.

Levodopa: more significant motor improvement but greater risk of later complications (fluctuations and dyskinesias)

Dopamine agonist: less marked motor response, but lower risk of motor complications. However, other complications occur.

Levodopa

This is the most effective medication to improve motor features. It reduces bradykinesia and rigidity though variable on tremor. It comes in a fixed dose combination with peripheral dopa decarboxylase inhibitor (PDI) carbidopa or benserazide ,

available in 1:4 (preferred) and 1:10 ratios (LD to PDI).

Comes as immediate release or controlled release (CR).

Start at low dose

Escalate to tolerable dose with minimal side effects

Starting low reduces nausea and increases compliance: ½ tablet daily increasing weekly by ½ tablet to initial target 100/25 q8hrs or 6 hrs

Common side effects:

- Short term: nausea, vomiting, dizziness, hypotension
- Long-term use – motor complications (motor fluctuations and dyskinesias)

Levodopa : motor fluctuations

Risk factors: young age, increased severity, long PD duration, high LD dose. 4 clinical patterns-Wearing off; Delayed on; Random On/Off; No on.

These motor fluctuations result from fluctuating plasma levels, intermittent delivery of LD to brain, pulsatile striatal dopamine stimulation and disease progression (insufficient LD dose), impaired or erratic absorption.

Treatment: depends on type: e.g. Wearing off: increase dose or reduce dose interval, or add COMT, MAO-B or DA.

Dyskinesias manifests as wriggling, writhing, choreiform movements or dystonia in any body part. Often not bothersome to patients.

Types (based on timing of occurrence)

- Peak dose
- Diphasic
- Off-state

Treatment: depends on type. E.g. Peak dose: reduce dose of LD. Off state: increase LD dose.

Dopamine agonist

This is recommended as initial therapy in early PD

Types: ergot derived: bromocriptine, pergolide, cabergoline, lisuride

non-ergot derived: apomorphine, piribedil, pramipexole, ropinirole, rotigotine

All oral except apomorphine (subcut) and rotigotine

(transdermal patch).

Side effects include

- Moderate or severe cardiac valvulopathy
- Serosal fibrosis (pleural, pericardial, retroperitoneal)
- Caution: avoid; screening required
- Impulse control disorders (pathologic gambling, binge eating, hypersexuality).
- Risk ↑ in young men, OCD, alcohol abuse.
- Daytime somnolence
- Peripheral edema
- Others: nausea, dizziness, hallucinations, constipation

Other treatments include

Monoamine oxidase b inhibitors

- E.g. Selegilene, Rasagiline
- May be used as monotherapy in early PD

Anticholinergics

- Should not be used as first line treatment in PD
- Increased frequency of neuropsychiatric and cognitive adverse side effects (especially in elderly)

Amantadine

- Weak antiparkinsonian effect
- Useful in treating levodopa-induced dyskinesias

Catechol-o-methyl transferase inhibitor (entacapone)

- Added to levodopa/carbidopa to prolong effect (reduce 'off' time) by about 1.5 hours/day
- Prevents peripheral levodopa and central dopamine metabolism.

Treatment of Non-motor symptoms

Constipation

Fibre supplements (e.g. methylcellulose)
Osmotic laxatives (e.g. lactulose)
Short-term irritant laxatives

Orthostatic Hypotension

Review medications
Fludrocortisone 0.1mg
Midodrine

Urinary sypmtoms

Screen for and treat any UTI
Anticholinergics may be used e.g oxybutinin

Anxiety

Benzodiazepines (diazepam, lorazepam, clonazepam); SSRIs (fluoxetine, sertraline, paroxetine, etc. Start at low doses.)

Rem-sleep behavioural disorder

Benzodiazepines (clonazepam, with caution)

Hypersalivation (sialorrhea)

Atropine drops (1% drops 1-2 drops at night or b.d. under the tongue may be useful)

Dementia

- Discontinue potential aggravating drugs: *anticholinergics, amantadine, TCAs*
- Add cholinesterase inhibitors: *rivastigmine, donepezil, or galantamine*

Psychosis

- Reduce polypharmacy
- Add atypical antipsychotics: *quetiapine, (clozapine)*
- **Typical antipsychotics, olanzapine, risperidone, aripripazole worsen parkinsonism.**

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