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A REVIEW ON PARKINSON'S DISEASE

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ABSTRACT

Parkinson's disease (PD) is the most common neurodegenerative disorders characterized by a neuronal accumulation of the presynaptic protein synuclein and by variable degrees of parkinsonism, defined as a paucity and slowness of movement (bradykinesia), tremor at rest, rigidity, shuffling gait, and flexed posture. Nearly all forms of parkinsonism result from a reduction of dopaminergic transmission within the basal ganglia. . The incidence of PD is between 8 and 18 per 100,000 person in years. Prevalence in India is ab70/100,000 population and this is lower than that reported in the West. Most PD cases occur sporadically and of unknown cause. Twin studies suggest that environmental factors likely play the more important role in patient older than 50 years, with genetic factors being more important in younger patients. In PD dopaminergic and other cells die due to a combination of factors including: Genetic vulnerability, Oxidative stress, Proteosomal dysfunction, Environmental factors. Many risk factors and protective factors have been proposed, sometimes in relation to theories concerning possible mechanisms of the disease. None have been conclusively related to Parkinson's disease by empirical evidence. Therapy in PD are to maintain function and quality of life and to avoid drug-induced complications. This is obtained through the use of drugs that either increase dopaminergic actions or diminish neuronal outflow from the striatum.

KEYWORDS: PD, signs and symptoms, pathogenesis, treatment.

INTRODUCTION

Parkinson's disease (PD) is a common adult-onset neurodegenerative disorder of dopamine depletion involving multiple motor and non-motor circuits of the basal ganglia. The cardinal features of the disease are characteristically motor in nature (resting tremor, bradykinesia, rigidity and postural instability), changes in cognition, mood and emotion are common. A wide range of neuropsychiatric disturbances commonly occurs in patients with Parkinson's disease.[1] Neuropsychiatric disturbances contribute considerably to reduced quality of life, distress for the care giver and increased risk for admission to nursing home in patients with Parkinson's disease.[2] Parkinson's disease should be viewed nowadays as a complex disorder, characterised by motor signs and by a broad and challenging range of neurological and psychiatric symptoms.[3]

This common disease, known since ancient times, was first cogently described by James Parkinson in 1817. In his words, it was characterizied by "involuntary tremulous motion , with lessened muscular power, in parts not in action and even when supported; with a propensity to bend to trunk forward , and to pass from a walking to a running pace, the senses and intellect being uninjured."[17]

Epidemiology

Parkinson's disease (PD) is the second most common neurodegenerative disorder after Alzheimer's disease and is expected to impose an increasing social and economic burden on societies as population's age. The prevalence of PD in industrialised countries is generally estimated at 0.3% of the entire population.[4] PD is more common in the elderly and prevalence rises from 1% in those over 60 years of age to 4% of the population over 80. The mean age of onset is around 60 years, although 5–10% of cases, classified as young onset, begin between the ages of 20 and 50.[5] Some studies have proposed that it is more common in men than women, but others failed to detect any differences between the two sexes. The incidence of PD is between 8 and 18 per 100,000 person in years. Prevalence in India is about 70/100,000 population and this is lower than that reported in the West.[15]

Many risk factors and protective factors have been proposed, sometimes in relation to theories concerning possible mechanisms of the disease. None have been conclusively related to Parkinson's disease by empirical evidence. When epidemiological studies have been carried out in order to test the relationship between a given factor and Parkinson's disease, they have often

been flawed and their results have in some cases been contradictory. The most frequently replicated relationships are an increased risk of Parkinson's disease in those exposed to pesticides, and a reduced risk in smokers.[4]

Clinical Signs and Symptoms

Motor Manifestations

PD is a chronic, progressive neurologic disease. It presents with four cardinal motor manifestations:

- tremor at rest
- rigidity
- bradykinesia (or slowing of movement)
- postural instability

Not all patients initially present with all of the classic signs of the disorder, there may be only one or two. The first complaint is one of motor weakness or stiffness, and the cause is commonly misdiagnosed. Postural deficits and tremor may soon emerge, prompting a reconsideration of the basis of the problem. It is important to note that the clinical diagnosis of Parkinson's disease is made on the basis of a medical history and neurologic examination. There is currently no laboratory test that can definitely establish a diagnosis. Even neuroimaging, which can be used to obtain an estimate of dopamine loss is imperfect and in any event is too expensive to be used as a routine diagnostic tool. As a result, it has been estimated that a significant number of individuals diagnosed as having Parkinson's disease fail to show the histopathologic hallmarks of the disease upon autopsy.[11]

Tremor at rest is one of the most characteristic features of the disease, occurring in 70% of patients.[14] Whereas it is not required for diagnosis, the prolonged absence of tremor in the course of a patient's illness should lead to the careful consideration of other neurologic conditions that can present with signs of parkinsonism, including the multiple system atrophies, progressive supranuclear palsy, corticobasal ganglionic degeneration, and others.[11]

Rigidity is a motor sign more often appreciated by the examining physician than the patient. It is detected as a resistance to passive movement of the limbs. It is often uniform in directions of flexion and extension (''lead pipe rigidity''), but there may be a superimposed ratcheting (''cogwheel rigidity'').

Bradykinesia refers to a slowness and paucity of movement; examples include loss of facial expression, which may be misinterpreted as a loss of affect, and associated movements such as arm swinging when walking. Bradykinesia is not due to limb rigidity; it can be observed in the absence of rigidity during treatment. When bradykinesia affects the oropharynx, it can lead to difficulties in swallowing, which in turn may cause aspiration pneumonia, a potentially life threatening complication.[12]

Postural instability is the most potentially dangerous, because it can lead to falls with resulting fractures. It is also one of the manifestations that responds less well to levodopa therapy.[13]

An additional motor feature of PD is the freezing phenomenon also referred to as ''motor block''. Most typical form, freezing occurs as a sudden inability to step forward while walking. It may occur at the beginning (''start hesitation''), at a turn, or just before reaching the destination. It is transient, lasting seconds or minutes, and suddenly abates.

PATHOGENESIS[21]

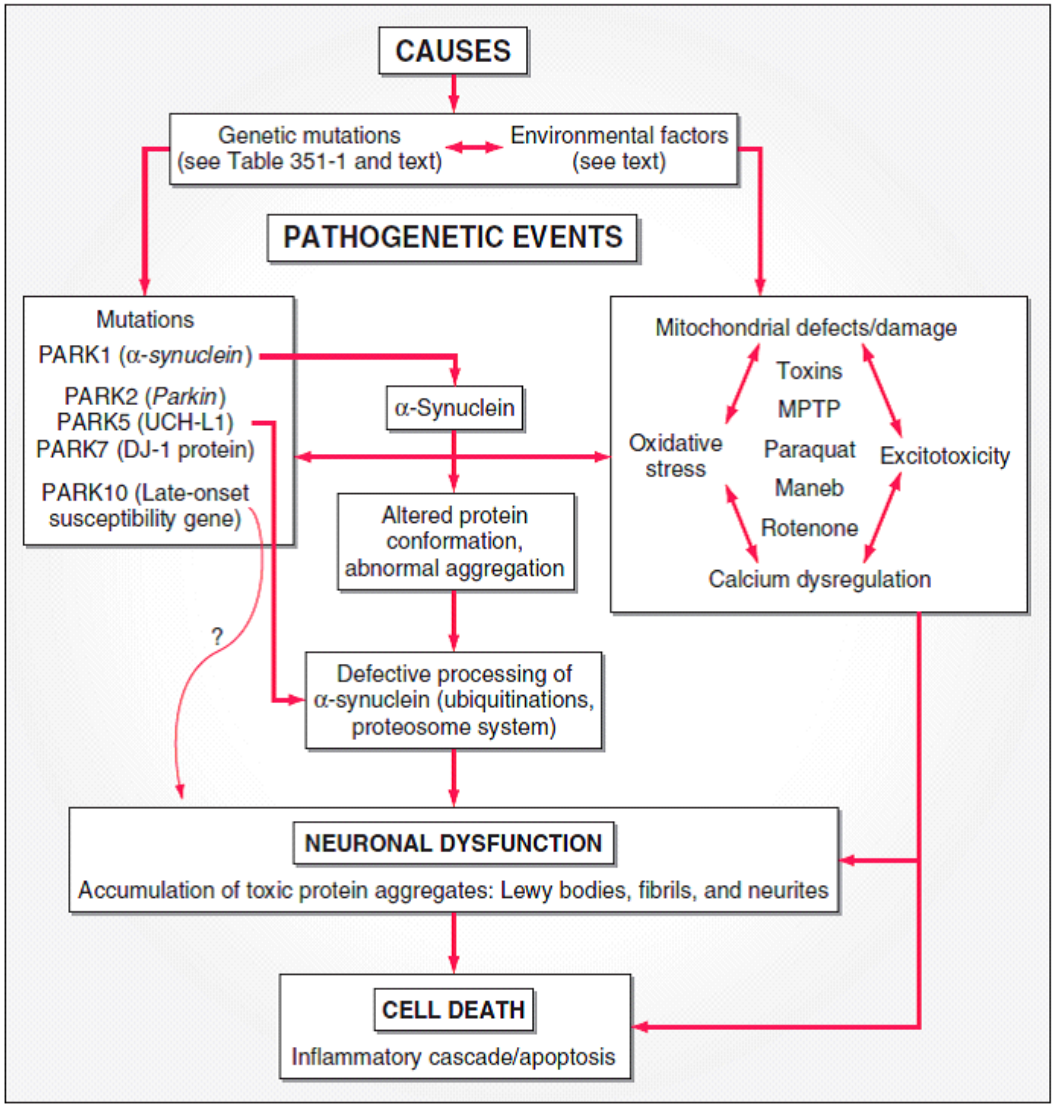
Most PD cases occur sporadically and of unknown cause. Twin studies suggest that environmental factors likely play the more important role in patient older than 50 years, with genetic factors being more important in younger patients. In PD dopaminergic and other cells die due to a combination of factors including:

- Genetic vulnerability
- Oxidative stress
- Proteosomal dysfunction
- Environmental factors

Oxidative stress appears to play an important role in the sporadic forms of PD. Endogenous sources of oxidative stress include the free radicals produced by the metabolism of dopamine and melanin. Additional stress may come from defects in mitochondrial complex one of the oxidative phosphorylation chain in patients with PD.

This defect has been detected in platelets and muscle and in postmortem tissue from the substantia nigra. Several toxins have been shown to cause oxidative toxicity and dopamine cell death in animal models of PD, further strengthening the above hypothesis. The most important of these are MPTP, a meperidine derivative, and rotenone, a commonly used insecticide. Both cause oxidative damage by inhibiting complex. In vitro, oxidative stress can lead to aggregation of synuclein and proteosomal dysfunction.

Proteosomal system abnormalities have also been described in the substantia nigra from sporadic cases of PD. The other factors of the selective dopamine neuron degeneration in PD are microglial activation, low-grade inflammation, and apoptosis, each a potential target for therapeutic intervention.

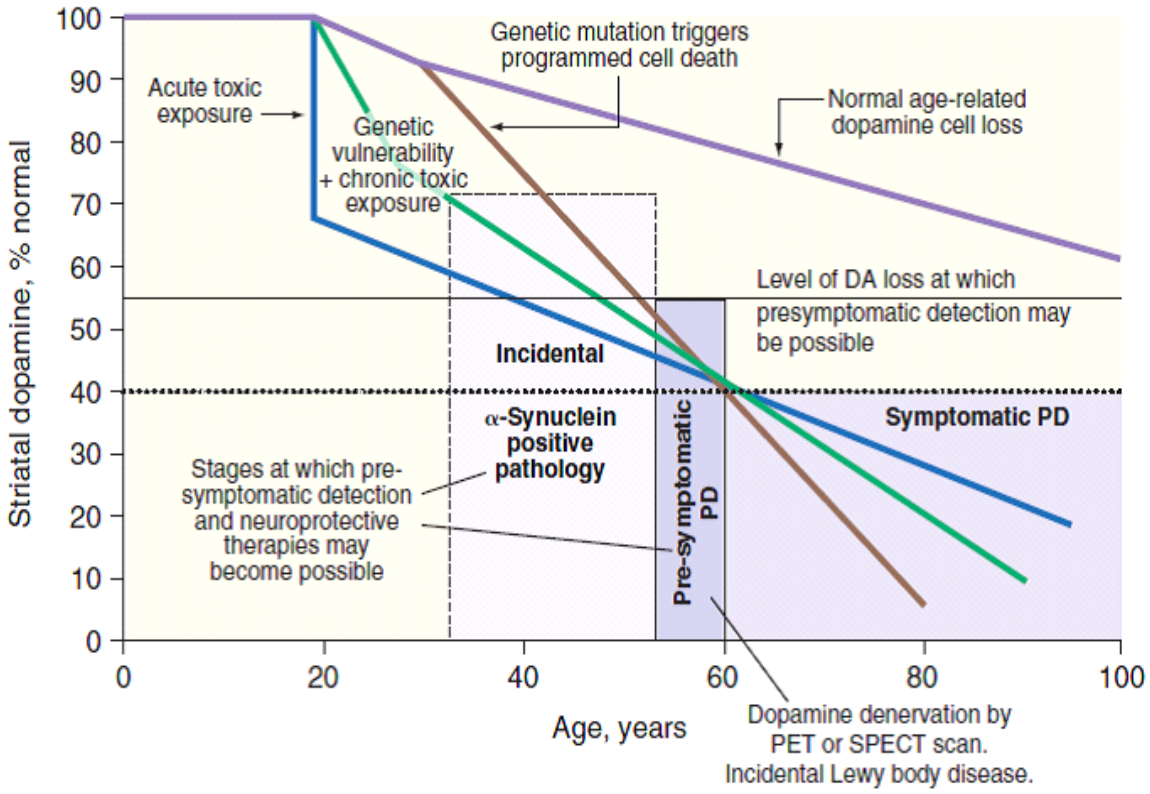

CAUSES
Genetic mutations (see Table 351-1 and text)
Environmental factors (see text)
PATHOGENETIC EVENTS
Mutations
PARK1 (α-synuclein)
PARK2 (Parkin)
PARK5 (UCH-L1)
PARK7 (DJ-1 protein)
PARK10 (Late-onset susceptibility gene)
α-Synuclein
Altered protein conformation, abnormal aggregation
Defective processing of α-synuclein (ubiquitinations, proteosome system)
?
Mitochondrial defects/damage
Toxins
MPTP
Oxidative stress
Paraquat
Excitotoxicity
Maneb
Rotenone
Calcium dysregulation
NEURONAL DYSFUNCTION
Accumulation of toxic protein aggregates: Lewy bodies, fibrils, and neurites
CELL DEATH
Inflammatory cascade/apoptosis

processes of the substantia nigra pars compacta (SNpc), other brainstem nuclei, and regions such as the medial temporal, limbic, and frontal cortices. LBs have a high concentration of synuclein and are the pathologic hallmark of the disorder. Mutations in the synuclein gene can cause familial PD by promoting the formation of synuclein positive filaments that aggregate into LBs and Lewy neurites.

This pathology may begin in the anterior olfactorynuclei and lower brainstem (glossopharyngeal and vagal nerve nuclei), with ascending brainstem involvement of the locus coeruleus, n. gigantocellularis, and the raphe, before extending to the magnocellular nuclei of the basal forebrain, the central nucleus of the amygdala, and the SNpc. Involvement of these nuclei may play a role in the non-motor (e.g., autonomic, sleep, emotional, and cognitive) and refractorymotor aspects (e.g., postural instability, gait, and bulbar disturbances) of PD.

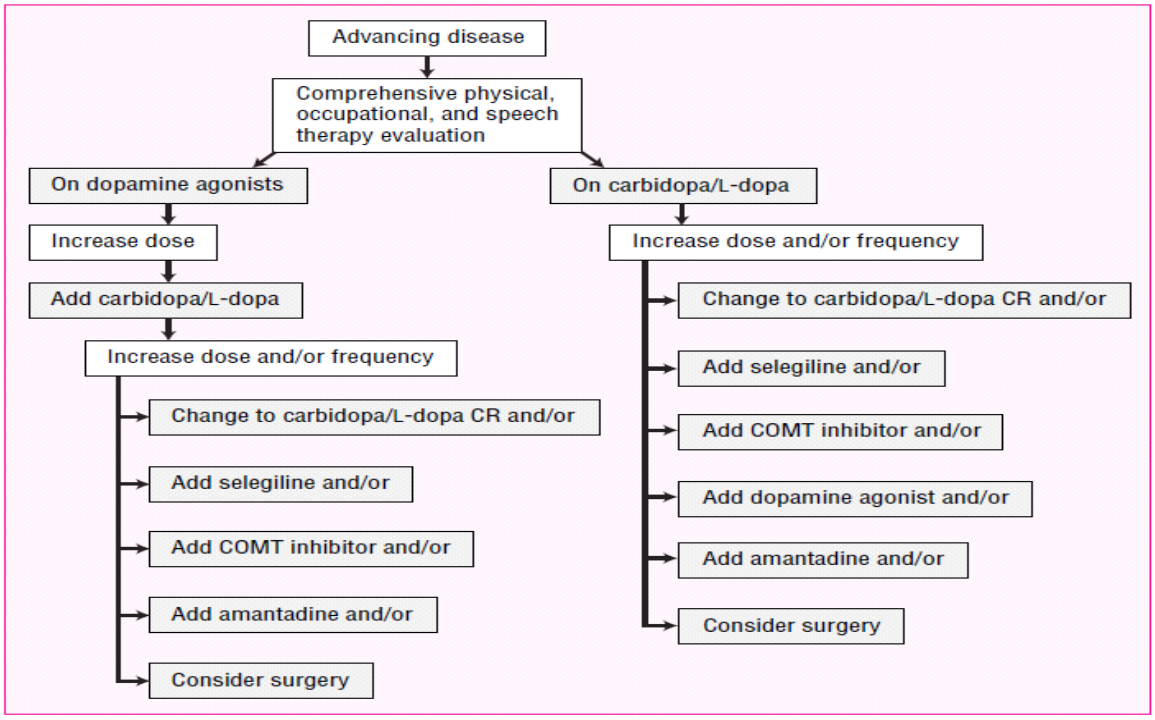
The biochemical consequence of dopaminergic cell loss in the SNpc is gradual denervation of the striatum, the main target projection for the SNpc neurons. Other target regions of these neurons include the intralaminar and parafascicular nuclei of the thalamus, the globus pallidus, and the subthalamic nucleus (STN).

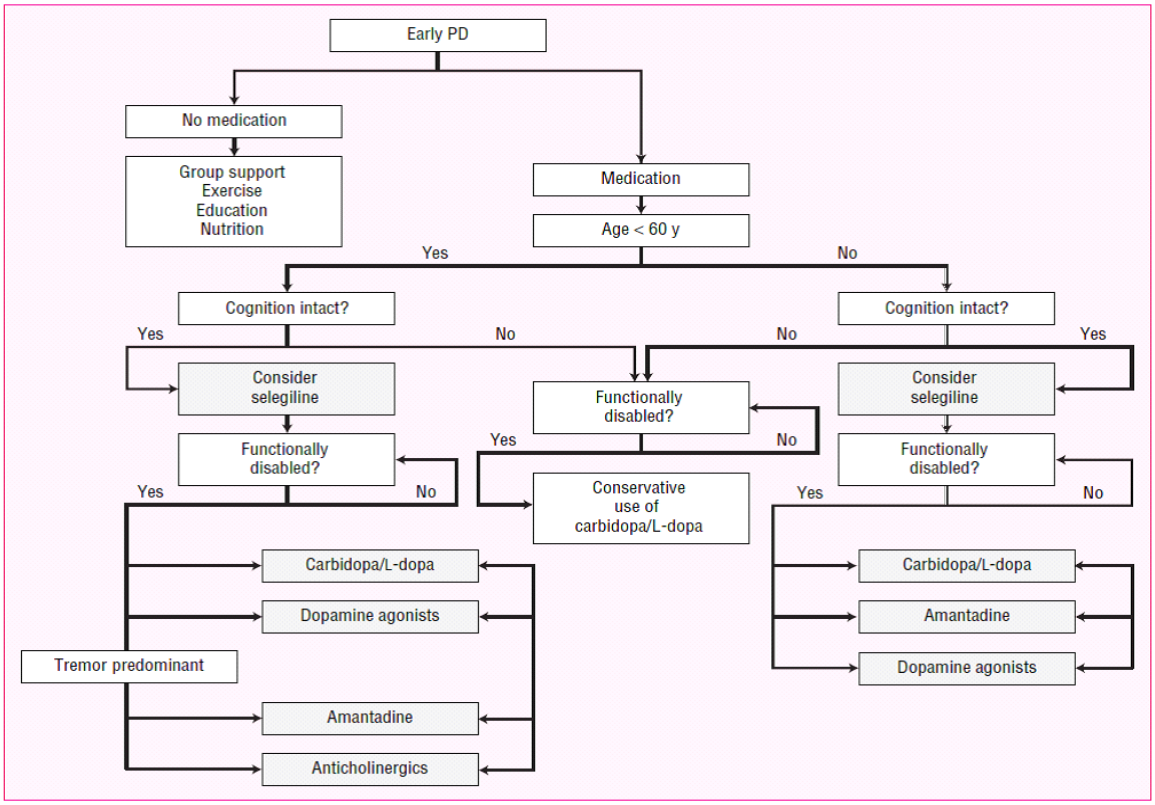
Dopamine denervation of the striatum leads to many of the motor symptoms of PD. Symptoms develop when striatal dopamine depletion reaches 50 to 70% of normal. Pharmacologic restoration of dopamine transmission is the basis for symptomatic drug treatment of PD.



of the GPi) and GPi DBS can help with severe dyskinesias and on/off fluctuations but is not as helpful for bradykinesia. Destructive lesions are immediate and permanent, whereas DBS requires lifelong maintenance. Transplantation of autologous adrenal medulla tissue was unsuccessful, as has been more recent experience in most cases of fetal tissue transplantation.

Algorithm for treating advanced IPD





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