PARKINSON'S DISEASE- A REVIEW

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ABSTRACT

Parkinson's disease is a disease of insidious onset. The symptoms usually come on slowly over time. (1). Parkinson's disease is a neurodegenerative disease that affects an area of the brain- Substantia nigra. This is age related and non-reversible disease. It mainly affects the motor system and to some extent non-motor system is also involved. Parkinson's disease is the second most common neurodegenerative disease after Alzheimer's disease. It is a progressive disease, which is usually slow. At the onset the most obvious are shaking rigidity, slowness of movements and difficulty with walking and writing. The main motor symptoms are collectively called Parkinsonism or Parkinson's syndrome. Non-motor symptoms are also seen. Thinking and behavioural problems may occur early. (2). Depression and anxiety are also common- occurs in more than one-third of Parkinson's disease. Dementia becomes common in the advanced stage of the disease. Other symptoms are sensory, sleep and emotional problems. The disease is more common in male than female by a ratio of 2: 1. There are two basic types of Parkinson's disease. They are-

(1) Idiopathic, and

(2) Secondary.

Idiopathic Parkinson's disease is more common. In idiopathic Parkinson's disease cause is not known, but genetic and environmental factors are involved. Those with a family history are more prone to suffer from the disease. However, no effective therapy exists till date. The treatment is directed to improve symptoms and slow the progress of the disease. As the disease progresses neurons continue to be lost, these medications become ineffective. Focus of current research is to increase awareness for Parkinson's disease and try to prevent the disease to occur and early diagnosis and management to improve quality of life of patients.

The aim is to describe pathophysiology and historical perspective and aware that person suffering from Parkinson's disease can live a normal life. An English doctor James Parkinson published the first detailed description of the disease- "An Essay of the Shaking Palsy" in 1817- the disease is named after him- Parkinson's disease.

KEYWORDS

Parkinson's Disease, Dopamine, International Treatment Rigidity.

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BACKGROUND

Onset of Parkinson's disease is insidious. The symptoms usually come on slowly overtime.⁽¹⁾ It is a neurodegenerative disease that affects mainly dopamine producing neurons of brain- a specific area, i.e. Substantia nigra. It is age related and non-reversible disease. Parkinson's disease typically occurs in people over the age of 60 yrs., of which about one percent are affected. 4% of population are over 80 yrs. When it occurs before the age of 50, it is called young onset Parkinson's disease.⁽²⁾ In 2015, Parkinson's disease affected about 6.2 million people and resulted in about 117,400 deaths globally.^{(3),(4)} More than one million are reported per year in India. The number of new cases per year is 8 to 18 per lakh persons. Males are affected more than females in a ratio of 2: 1.4. The average life expectancy following diagnosis is 7 to 14 years.⁽⁵⁾ The number of new cases of Parkinson's disease per year is between 08 - 18 per lakh people. Public awareness campaigns include World Parkinson's Day on the

birth day of James Parkinson- 11th April and the use of Red Tulip as the symbol of the disease.⁽⁶⁾ People with Parkinson's disease who increased the public awareness of the disease include actor Michael J. Fox, Olympic cyclist Davis Phinney and late professional boxer Mohammad Ali.

Parkinson's disease is the second most common neurodegenerative disorder after Alzheimer's disease. Sometimes Parkinson's disease is also called as a synucleinopathy due to accumulation of abnormal alpha-synuclein protein in the brain to distinguish it from other neurodegenerative diseases, e.g. Alzheimer's disease where the Tau protein accumulates in the brain. Clinical features also differ in synucleinopathy and tauopathies. Memory loss is common in Alzheimer's disease, but not common in Parkinson's disease. Slowness, tremor, stiffness and postural instability are main signs of Parkinson's disease, but not normal features of Alzheimer's disease. Many neurodegenerative diseases may present with atypical Parkinsonism, Parkinson's plus syndrome and some other features which distinguish it from Parkinson's disease e.g. Multiple sclerosis.⁽⁷⁾

Pathophysiology

A model of the motor circuit is described in normal condition and its alteration in Parkinson's disease is described since 1980 with some limitations. In this model, the basal ganglion normally exerts a constant inhibitory influence on a wide

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range of motor systems preventing them from becoming active at inappropriate time. Substantia nigra is divided into-

- 1) Substantia nigra compact have closely packed pigmented neurons, hence the name.
- 2) Substantia nigra reticulate have non-pigmented and loosely packed neurons.

Neurons of Substantia nigra compact secrete neurotransmitter dopamine and project to Caudate nucleus and Putamen nucleus. Dopamine promotes movements by direct and indirect pathways.

Dopamine promotes direct pathways, which is excitatory by action on D1 receptors. They increase inhibition; therefore, the cortical output is decreased-

Dopamine +D1 ↔ Stimulates Adenylyl Cyclase.

Dopamine inhibits the indirect pathways by action on D2 receptors. They decrease inhibition, therefore the cortical output increases and movements increases.

Dopamine +D2 ↔ Inhibits Adenylyl Cyclase.

Neostriatum is influenced by-

1. The excitatory effect of cholinergic fibres, and
2. The inhibitory effect of Dopaminergic fibres.

There is balance effect of these two opposite fibres for normal smooth functions of motor activity. The lack of Dopamine in Parkinson's disease reduces the inhibitory effect, so excitatory cholinergic fibres causes hyperkinetic features.

When a decision is made to perform a particular action, inhibition is reduced for the required motor system and it becomes active. Dopamine acts to facilitate this release of inhibition, so high levels of dopamine function tend to promote motor activity. But when level in low inhibition is not reduced, resulting in greater exertion of effort for any particular movement. In Parkinson's disease, dopamine level is reduced. This is due to cell death in Substantia nigra. The reason for this cell death is poorly understood, but involves the build-up of proteins into Lewy bodies in the neurons.

There are several mechanisms by which the brain cells could be lost. Widely accepted theory is abnormal accumulation of the protein 'alpha-synuclein' bound to ubiquitin in the damaged cells. This insoluble protein accumulates inside neurons forming inclusion body called Lewy bodies. These Lewy bodies may not cause cell death, instead it may be protective by sequestering the abnormal protein, so that it may not damage the cell. Other forms of 'alpha synuclein' (oligomers) that are not aggregated in Lewy bodies and Lewy neuritis may be the toxic form of the protein leading to cell death.⁽⁸⁾ Lewy bodies are present in cortical areas in persons suffering from dementia. Neurofibrillary tangles and senile plaques, characteristic of Alzheimer's disease are not common unless person is suffering from dementia.

Other mechanism of cell death include Proteasomal and lysosomal system dysfunction and reduced mitochondrial activity.⁽⁹⁾ Cell death may be related to oxidative stress,

protein aggregation but the mechanisms are not fully understood.

Aetiology

Cause of Parkinson's Disease-

1. Idiopathic or Primary- cause is not known, hereditary and environmental factors have role.
2. Secondary-
 1. Cerebral arteriosclerosis reduction in rate of cerebral blood flow.
 2. Complications of diseases- encephalitis, neurosyphilis, Wilson's disease etc.
 3. Complications of drugs- phenothiazine, reserpine.

Other Way of Classification

1. Impaired release of dopamine- idiopathic, drugs toxins.
2. Blockage of striatal dopamine receptors- phenothiazine.
3. Damage to striatal neurons- multisystemic disease.

Due to degeneration of substantia nigra and/ or Globus pallidus concentration of dopamine in nigrostriatal system is reduced.

Risk Factors

- Family history.
- Exposure to certain pesticides.
- History of head injury.

Reduced risk in Tobacco smokers and those who drink tea or coffee.^{(2),(10)} Exercise in middle age reduce the risk.⁽¹¹⁾

Staging of Parkinson's Disease

Braak staging of Parkinson's disease is based on pathological findings. According to this staging Lewy bodies first appear in the olfactory bulb, Medulla Oblongata and Pontine tegmentum. Individuals at this stage do not suffer from motor dysfunction motor symptoms and may have same non-motor symptoms such as less sense of smell or sleep disturbance or automatic dysfunctions. As the disease progresses, Lewy bodies develop in the Substantia nigra, areas of the midbrain and basal forebrain and finally in neocortex. These sites are the main places of neuronal degeneration in Parkinson's disease.

Hoehn and Yahr scale to gauge the progression of the disease over the years. The scale was originally implemented in 1967 and include stages. The stages are:-

- 0) No sign of Parkinson's disease.

Advanced Parkinson's Disease

Later some modification was done and known as modified Hoehn and Yahr scale.

Symptoms develop when a significant number of neurons of substantia nigra are lost or not working properly. Clinical features of Parkinson's disease are-

Hyperkinetic Features

- Resting tremor.
- Rigidity- Leadpipe or cogwheel rigidity.⁽¹²⁾

Hypokinetic Features

- Hypokinesia= bradykinesia= akinesia.
- Mask-like face.

- Micrographia.
- Festinate gait or shuffling gait.
- Retropulsion/ lateropulsion.
- Pill-rolling movements.
- Loss of associated movements that occurs normally subconsciously, e.g. swinging of arms during walking.

Non-Motor Functions

- Sleep disturbance.
- Emotional disturbance.
- Dementia.

Diagnosis

Is clinical. Resting tremor, rigidity- lead-pipe or cogwheel rigidity, Hypokinesia or bradykinesia, Mask-like face, Micrographia, Festinate gait. Retropulsion or lateropulsion. Pill rolling movements pin point the diagnosis. Computed tomography (CT) scans usually do not help in diagnosis. MRI has become more accurate in diagnosis of the disease, specifically through iron-sensitive T2 and SWI sequences at a magnetic field strength of at least 3T, both of which can demonstrate absence of the characteristic “swallowtail” imaging pattern in the dorsolateral Substantia nigra.⁽¹³⁾

Treatment

There is no cure, treatment is aimed to improve symptoms without slowing or halting progress of the disease. There is no evidence that acupuncture and practice of Yoga, Qigong or Tai Chi have any effect on the course of the disease or symptoms. Several nutrients have been proposed as possible treatments, but there is no evidence that vitamins or food additives improve symptoms.

Medical

Dopaminergic medication is given. Dopamine cannot enter into brain tissue due to presence of blood brain barrier, so it is ineffective. Levodopa is used which cross the blood brain

barrier and is converted into dopamine inside brain and exert its effect.

Surgical

Some surgeries- Stereotactic neurosurgery are performed in advance cases when medical treatment failed with variable results. Globus pallidus or its connection with Substantia nigra is removed to reduce the symptoms of Parkinson's disease.

Physiotherapy

Is used to overcome the deficiency. Gentle exercise will help in many cases.

Future

A task force of the International Parkinson and Movement Disorder Society (MDS) has proposed diagnosis criteria for Parkinson's disease as well as research criteria for the diagnosis of the disease, but require wide acceptance against the more established criteria.^{(14),(15)} Investigation is going on to identify biomarkers of Parkinson's disease, but that will help in early diagnosis and slow progression of the disease. Agents currently under investigation are anti-apoptotics (Omigapil), anti-glutamatergics, monoamine oxidase inhibitors (Selegiline), promitochondrials (Coenzyme Q10, creatine), calcium channel blockers (Isradipine) and growth factors (GDNF).⁽⁹⁾ A vaccine that primes the human immune system to destroy alpha-synuclein, PD01A (developed by Austrian company, Affairs), has entered clinical trials in humans. It has been proposed that effective treatments may be developed by use of induced pluripotent stem cells taken from adults.⁽⁴⁾

Prognosis

Parkinson's disease is not fatal, but complications of disease may be serious. The centre for disease control and prevention (CDC) rated complications of Parkinson's disease as the 14th cause of death in the United States. In India such data is not available, but complications like injury due to fall or pneumonia are often fatal. The average life expectancy following diagnosis is 7 to 14 years.⁽⁵⁾

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