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Parkinson's Disease

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Abstract

Parkinson's disease is a neurodegenerative condition that commonly afflicts the elderly population. It is responsible for high morbidity and disabilities in old age. Understanding the pathophysiology of the disease will help in better management of patients with Parkinsonism. Newer anti-parkinsonian drugs achieve better control of symptoms with fewer side effects. Complications of the disease include hypostatic pneumonia and head injuries due to frequent falls.

Keywords: Parkinsonism; Levodopa; Dopamine; Agonists

Introduction

Parkinson's disease is a neurodegenerative condition that presents clinically as rest tremor, rigidity and bradykinesia. Apart from these cardinal symptoms, a gamut of motor and non-motor features can be attributed to this condition. The motor features are mask like facies, reduced eye blinking and hypophonia. The non-motor features include mood changes, sleep disturbance, autonomic dysfunction and cognitive impairment.

The disease is commonly seen in individuals above the age of 60 years. There is no gender predilection in Parkinson's disease. Complications like immobility and tendency to fall are responsible for morbidity due to parkinsonism.

Pathophysiology

The basic pathologic change that occurs in Parkinson's disease is degeneration of dopaminergic neurons in the substantia nigra. This leads to a reduction in dopamine production from the nigral cells. Apart from this, there is deposition of Lewy bodies (intra-cytoplasmic hyaline inclusions) in the substantia nigra. Reduced dopamine synthesis is responsible for symptoms like bradykinesia in Parkinson's disease.

Nuclei in the basal ganglia are connected to neurons in the motor cortex and help in the regulation of motor function. Input to the basal ganglia occurs from the striatum. The output regions of the basal ganglia include the substantia nigra and globus pallidus. There is an inhibitory effect on neurons in the brainstem and thalamus due to output from the basal ganglia. The brainstem and thalamic neurons are also connected to the motor neurons of the spinal cord and the cerebral cortex. Thus, they also play a role in the regulation of motor function.

Due to dopamine depletion in the basal ganglia, there is an excitatory effect on the subthalamic nucleus and globus pallidus. This leads to thalamic and motor cortical inhibition which is responsible for the clinical features of Parkinson's disease.

Etiology and Pathogenesis

A majority of cases of Parkinson's disease are sporadic in nature and their cause is not known. A small number of cases are familial in nature. In familial cases, genetic mutations have been identified that can cause disease in association with exposure to an environmental factor.

There is currently no evidence to link any environmental factor in the pathogenesis of Parkinson's disease. However, studies have suggested that there is an increased risk of the disease in persons who have been exposed to pesticides, while there is a reduced risk in those consuming nicotine and caffeine.

A compound called methyl-phenyl-tetrahydropyridine (MPTP) was implicated in the causation of severe Parkinsonism in young drug addicts. MPTP is metabolized to a mitochondrial toxin in the central nervous system. This toxin causes damage to the dopaminergic neurons. However, there is no current evidence to demonstrate the role of MPTP in sporadic cases of Parkinson's disease.

The factors responsible for neuronal cell death in Parkinson's disease are oxidative stress, inflammation, protein aggregation, excitotoxicity and mitochondrial dysfunction. Cell death occurs due to signal-mediated apoptosis. A proper understanding of the mechanisms leading to neuronal cell death can help in the development of neuroprotective drugs in the future for better management of the disease.

Clinical Features

The symptoms of Parkinson's disease are unilateral in the early stages of the disease. Bilateral involvement is common in the advanced stages of the disease. Resting tremor is a common symptom and it is usually seen as flexion/extension of the fingers and abduction/adduction of thumb in the upper limb. Tremor can involve the lower limbs and tongue over a period of time. The tremor is usually present at rest and is decreased on movements.

Another common symptom is bradykinesia which is defined as slowness in the initiation of movements. There is difficulty in performing fine movements with fingers. Patients with Parkinson's disease have a typical gait. They find difficulty in initiation of walking,

take short steps and have reduced arm swing while walking. They can lose balance while turning which may result in falls during walking.

The cardinal finding in patients with Parkinson's disease is cogwheel rigidity that is usually seen in the upper limbs. Patients also have a mask-like expressionless face and reduced blinking. Glabellar tap sign is positive in such patients. Speech becomes soft and difficult to understand, which becomes indistinct gradually. As the disease progresses, postural reflexes become impaired that can lead to inadvertent falls and subsequent injuries.

Investigations

The diagnosis of Parkinson's disease is based only on clinical findings. Investigations are indicated if patients have unusual features of the disease. In such cases, investigations are needed to rule out other causes of parkinsonism.

Wilson's disease needs to be ruled out if patients present with parkinsonian features before the age of 40 years. Neuro-imaging of the brain (MRI brain) may show degenerative changes in the basal ganglia in patients with Wilson's disease.

MRI of the brain is indicated in patients with primary parkinsonism if there are signs of pyramidal or cerebellar involvement.

Management

Management of Parkinson's disease can be broadly divided as follows-

Pharmacologic therapy

Surgical management

Physiotherapy and speech therapy

Management of non-motor and non-dopaminergic features

Pharmacologic therapy

Levodopa: Levodopa is a precursor of dopamine and is the drug of choice in the management of Parkinson's disease. Usually, it is combined with a peripherally acting dopa-decarboxylase inhibitor. On oral administration, levodopa undergoes peripheral decarboxylation to release dopamine. As a result, only a small amount of dopamine reaches the brain. Also, side effects like nausea and vomiting occur due to peripheral decarboxylation of the drug.

Hence, levodopa is combined with a peripheral decarboxylase inhibitor like carbidopa or benserazide to prevent the occurrence of side effects and to ensure that adequate amount of dopamine reaches the brain. Nausea and vomiting due to levodopa can be minimized with the help of domperidone.

Levodopa provides symptomatic improvement of the motor features of the disease. There is improvement of bradykinesia, rigidity and tremor in patients with levodopa. It helps in improving the quality of life in patients with Parkinson's disease. Carbidopa/levodopa combination is available as 10/100 and 25/100 mg. It can be given orally 3-4 times in a day. The maximum dose of levodopa that can be administered is 1000 mg/day.

Long-term treatment with levodopa leads to the development of motor complications and involuntary movements. These are termed as dyskinesias. Dyskinesias can occur as choreiform movements, dystonia or myoclonus. They are seen commonly when the drug reaches its peak plasma concentration (peak-dose phenomenon).

Diphasic dyskinesias occur when the action of levodopa begins and when it starts wearing off. They manifest as transient, stereotypic, rhythmic movements predominantly involving the lower limbs. Management is by increasing the dose of levodopa in such patients.

There can be sudden and unpredictable changes in response to levodopa therapy over a period of time due to progression of the disease. This is manifested as complex motor fluctuations. Here, there is an alternation of disabling dyskinesias and severe Parkinsonism (on-off phenomenon). The exact cause of levodopa-induced motor fluctuations is not known. They are more commonly seen in patients with severe disease and with higher doses of levodopa.

Levodopa induced dyskinesias can be due to non-physiologic levodopa replacement in the striatum. In the normal individual, dopamine in the striatum is maintained at a constant level. In patients with Parkinsonism, there is degeneration of dopamine producing neurons in the striatum. As a result, striatal dopamine level becomes dependent on the peripheral availability of levodopa. Oral levodopa does not lead to physiologic levels of dopamine in the striatum. This causes the dopamine receptors to be exposed to alternating high and low concentrations of dopamine. Ultimately, this leads to molecular changes in the striatal neurons that is responsible for levodopa induced motor complications. Management of levodopa induced dyskinesias is by administration of levodopa in smaller but more frequent doses.

Common side effects of levodopa are nausea and vomiting. Behavioural changes can be seen in patients taking levodopa. They can manifest as drug (levodopa) craving and hypersexuality.

Dopamine agonists: This group of drugs act on the dopamine receptors in the brain. They are less efficacious than levodopa. They can be used to improve motor function and decrease the 'off' period in patients with motor fluctuations. These drugs are less likely to induce dyskinesias or cause dose fluctuations as seen with levodopa.

Dopamine agonists can be ergot derivatives like bromocriptine, pergolide and cabergoline. These can be associated with fibrosis of the cardiac valves and hence are not preferred for the management of Parkinsonism.

Non-ergot dopamine agonists include pramipexole, ropinirole and rotigotine. Ropinirole and pramipexole can be given orally thrice daily or once daily as an extended-release preparation. Rotigotine is available as a trans-dermal patch and can be applied to the skin once daily. Apomorphine is a parenteral dopamine agonist and can be administered subcutaneously or as a continuous infusion. It has the advantage of reducing the 'off' period and dyskinesias in patients with advanced disease.

Pramipexole can be started as 0.25 mg tablets thrice daily and increased to a maximum dose of 1 mg thrice daily. Ropinirole is started at a dose of 6 mg/day and can be given till the maximum dose of 24 mg/day.

Side effects of dopamine agonists are nausea and vomiting that can be controlled with domperidone. Serious side effects include hallucinations, cognitive impairment, sleep attacks, pathologic gambling and hypersexuality.

COMT inhibitors: Catechol-O-methyltransferase (COMT) is an enzyme that is responsible for the metabolism of levodopa. Inhibition

of COMT will increase the half-life of levodopa and its availability in the striatum. Hence, COMT inhibitors decrease the 'off' period and increase the 'on' period in patients with motor fluctuations.

Examples of COMT inhibitors are entacapone and tolcapone. Entacapone is given orally as 200 mg in combination with levodopa. Tolcapone is initiated as 100 mg thrice daily orally and can be increased to a maximum dose of 200 mg thrice daily.

Side effects due to COMT inhibitors are nausea, vomiting and an increase in dyskinesias. Serious side effects like hepatotoxicity and diarrhea are commonly seen with tolcapone, but not with entacapone.

MAO-B inhibitors: Monoamine oxidase type B (MAO-B) inhibitors block the metabolism of dopamine in the brain and lead to increased concentration of dopamine in the neuronal synapses. They can be used alone in patients with early disease or can be combined with levodopa in patients with motor fluctuations to decrease the 'off' period. This group of drugs has some neuro-protective effect. It prevents further oxidative stress to the surviving dopamine producing neurons in the substantia nigra.

Drugs that belong to this group are selegiline and rasagiline. Selegiline is given orally as 5 mg twice daily while rasagiline is administered orally as 1 mg/day.

Surgical management: The commonly employed surgical technique for management of patients with Parkinson's disease is deep brain stimulation (DBS). In this procedure, an electrode is placed in the sub-thalamic nucleus or the globus pallidus. This electrode is then connected to a stimulator that is inserted subcutaneously over the chest wall. The technique mimics the effects of a brain lesion without causing an actual lesion.

DBS is relatively safe and can be used for performing procedures bilaterally as it does not involve creation of any lesion in the brain. It helps in improving dyskinesias and 'off' period in patients with Parkinsonism. However, there is no improvement in clinical features that do not show any response to levodopa. Also, DBS does not prevent the development or progression of non-dopaminergic features of the disease like dementia and falls.

DBS is indicated in patients with levodopa-induced motor complications that cannot be controlled with modification of the drug. Complications of the procedure are hemorrhage and infection during surgical insertion of the electrode, lead displacement, speech abnormalities and paresthesias.

Physiotherapy and speech therapy

Active and passive physiotherapy leads to an improvement in the functional physical capacity of patients with Parkinson's disease. Physiotherapy helps in decreasing muscle rigidity while speech therapy is helpful for patients with dysarthria and dysphonia.

Management of non-motor and non-dopaminergic features

The common non-dopaminergic features of Parkinson's disease are depression, psychosis, dementia, autonomic dysfunction and sleep disturbances.

Depression is seen in approximately 50% of patients with Parkinson's disease. It can be treated with anti-depressants like selective serotonin reuptake inhibitors (SSRIs).

Psychosis in patients with Parkinson's disease commonly manifests as visual hallucinations. It can be managed with the help of atypical neuroleptics like clozapine or quetiapine.

Dementia is a common problem in a large majority of patients with Parkinson's disease. Such patients usually have impairment of cognitive function and attention. All drugs used in the management of Parkinson's disease can cause cognitive impairment. Levodopa in the lowest possible dose is recommended for patients with cognitive dysfunction. Anticholinesterase drugs like donepezil and rivastigmine can be useful for improving cognitive function in patients with dementia.

Autonomic disturbances seen in patients with Parkinson's disease are constipation, sexual dysfunction and orthostatic hypotension. Constipation can be managed with a high fibre diet and plenty of oral fluids. If the problem persists, then laxatives can be tried. Sexual dysfunction in males can be treated with 5-phosphodiesterase inhibitors like sildenafil. Management of orthostatic hypotension can be done by addition of extra salt in the diet or by administration of low doses of fludrocortisone.

Sleep disturbances like fragmentation of normal sleep, daytime somnolence and disturbances in rapid eye movement (REM) sleep are commonly encountered in patients with parkinsonism. Benzodiazepines like clonazepam can help in the management of sleep abnormalities in such cases.

Stem cell therapy in Parkinson's disease

Transplantation of new dopamine generating cells into the substantia nigra can be an important treatment option in Parkinson's disease. This concept has formed the basic premise for stem cell therapy in Parkinsonism [1,2].

Embryonic stem (ES) cells can undergo in vitro proliferation and differentiation into various cell lineages in various cell culture conditions [3,4]. In this regard, mouse ES cells have been used as a source of transplantable tissue in various studies [5].

Deacon et al showed that ES cells have a capacity to undergo differentiation into dopamine producing neurons when they are grafted to the brain [6]. However; it was not possible to study the functional effects of the engrafted cells. This was because a large number of cells were used in the study which proliferated into big teratomas. These teratomas outgrew the target areas.

Mc Kay et al described the in vitro generation of dopaminergic neurons from mouse ES cells [7]. In this study, 30% dopamine differentiation was achieved by subjecting the stem cells to treatment with fibroblast growth factor 2 (FGF2), sonic hedgehog (SHH), fibroblast growth factor 8 (FGF8) and ascorbic acid. These dopamine producing neurons have been shown to have functional effects in rodent models of Parkinson's disease [8,9].

Neural progenitor cells (NPCs) are multipotent cells which can give rise to neurons, astrocytes and oligodendrocytes. They are usually obtained from the fetal or adult brain [10,11]. Some NPCs can undergo differentiation into dopamine producing neurons, but they have shown no benefits in a rodent model of Parkinson's disease [12].

In a majority of studies conducted on stem cell therapy for Parkinson's disease, cells have been grafted in an ectopic target area instead of the substantia nigra. This type of engraftment was necessitated because the dopamine producing neurons did not show

positive effects when they were placed in the substantia nigra. New investigational techniques that are being tried are grafting of stem cells to many target sites in the basal ganglia region [13].

Atypical and secondary Parkinsonism

Atypical Parkinsonism is a group of neurodegenerative disorders that are characterized by extensive neurodegeneration as compared to primary Parkinson's disease. Features of atypical parkinsonism include absence of rest tremor and early speech impairment. These clinical features show little or no improvement with levodopa.

Atypical parkinsonism includes the entities of multiple-system atrophy, progressive supranuclear palsy, corticobasal ganglionic degeneration and frontotemporal dementia.

Multiple-system atrophy (MSA) is an entity that presents as a combination of parkinsonian, cerebellar and autonomic features. It can be divided into a cerebellar type (MSA-c) or a parkinsonian type (MSA-p). Patients with MSA present with signs of cerebellar disease and early autonomic dysfunction.

Progressive supranuclear palsy (PSP) manifests as eyelid apraxia and restriction of eye movements. Gait disturbance, dysphagia, dysphonia and dementia are also commonly seen in patients with PSP.

Corticobasal ganglionic degeneration and frontotemporal dementia are less common forms of atypical parkinsonism.

Causes of secondary parkinsonism are head trauma, toxins, encephalitis and drugs. Toxins implicated in the development of secondary parkinsonism include manganese and carbon monoxide. Infections of the central nervous system (CNS) like viral encephalitis can be responsible for secondary parkinsonism. Drugs that are anti-dopaminergic or have dopamine-blocking action can lead to secondary parkinsonism. Examples of drugs which can cause secondary parkinsonism are neuroleptics, metoclopramide and chlorperazine.

Summary

Parkinson's disease is a common neurodegenerative disorder. It usually presents as tremor in patients above the age of 60 years. Rigidity and bradykinesia are common findings on neurologic examination. The basic pathology in Parkinson's disease is depletion of dopamine producing neurons in the substantia nigra due to a variety of reasons.

Levodopa is the drug of choice in the management of patients with Parkinsonism. Newer groups of drugs like COMT inhibitors and dopamine agonists are also helpful in relief of symptoms. Physiotherapy and speech therapy help can decrease the morbidity of patients suffering from Parkinson's disease.

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