Parkinson Diseases

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1 Introduction

Parkinsonism is a broad term referring to various neurodegenerative diseases that manifest with motor symptoms such as rigidity, tremors, and bradykinesia. Parkinson disease accounts for approximately 80% of cases, while the remainder comprises a collection of other neurodegenerative diseases with similar motor symptoms. Diagnosis of the disease involves clinical assessment and ruling out alternative causes. The usual treatment for Parkinson disease involves medications that help manage the symptoms. Although Parkinson disease typically shows a positive response to levodopa therapy, secondary causes of parkinsonism generally do not respond to this treatment.

James Parkinson was the first author to describe a case series of 6 patients in an essay titled "An Essay on the Shaking Palsy", published in 1817.

Although parkinsonism is a characteristic feature of Parkinson disease, similar symptoms can also arise from other neurodegenerative disorders, specific brain lesions, head trauma, medications, metabolic conditions, and exposure to toxins.

2 Classification

2.1 Parkinson's Disease

Parkinson disease is the most common cause of parkinsonism, which gradually manifests as asymmetric parkinsonism. Due to neuronal degeneration, dopaminergic neuronal loss is evident in the midbrain, resulting in a decrease in dopamine levels, especially in the post-commissural putamen and other regions of the basal ganglia.

Although Parkinson disease typically shows a positive response to levodopa therapy, secondary causes of parkinsonism generally do not respond to this treatment, which include the below-mentioned conditions.

2.2 Specific Secondary Causes of Parkinsonism

Normal pressure hydrocephalus Normal pressure hydrocephalus (NPH) presents with the classic triad of ataxia, urinary incontinence, and dementia. Parkinsonism may sometimes be the presenting symptom in NPH. The earliest reporting of parkinsonian features and hydrocephalus included the involvement of posterior fossa tumors.

Vascular parkinsonism Critchley was the first to describe vascular parkinsonism as a distinct entity in 1929. Previously, clinicians referred to the disorder as arteriosclerotic parkinsonism, lower-body parkinsonism, and vascular pseudo-parkinsonism.

Vascular Parkinsonism usually occurs due to an underlying vascular disorder, most commonly hypertension, that leads to subcortical infarcts, white matter ischemia, and large vessel infarcts. Diffuse white matter ischemic lesions that present bilaterally can destroy thalamocortical functioning, reducing the impulses sent to the higher centers via the basal ganglia and causing disruptions in motor movements. Imaging studies usually support the symptomatic diagnosis of vascular parkinsonism.[6]

Drug-induced parkinsonism Medications that block the dopamine receptors and interrupt the transmission of dopamine are known to cause secondary parkinsonism. The risk factors for developing this type include the route, potency, and dose of the drug administered. Individuals who are on medications administered via the intramuscular (IM) route or in the form of suppositories are more likely to develop drug-induced parkinsonism, especially at lower doses, as compared to administration via the intravenous (IV) route. At the same time, a drug with higher potency is more likely to cause parkinsonism when compared to a drug with lower potency. Parkinsonism usually occurs at higher doses of medications since dopamine receptor blockade occurs at higher doses.

Toxin-induced parkinsonism Prolonged exposure to heavy metals and industrial toxins can result in parkinsonian features. Toxins result in vast neurological damage, resulting in parkinsonism as compared to that seen in Parkinson disease.

Chronic traumatic encephalopathy A repeated head injury can often present with parkinsonian features.

Other causes of secondary parkinsonism include brarin tumors, juvenile parkinsonism, hypoxia, postencephalitis conditions, and metabolic disorders. Additional genetically determined causes of parkinsonism, such as juvenile-onset Huntington disease or certain spinocerebellar ataxias, may initially present clinically as a rigid-akinetic syndrome resembling parkinsonism.

Parkinson-plus syndromes Parkinson-plus syndromes include multiple system atrophy, corticobasal degeneration, and progressive supranuclear palsy.

3 Epidemiology

3.1 Parkinson Disease

Parkinson disease usually affects around 1 to 2 individuals per 1000 in the population at any given time. This disease is uncommon in individuals aged 50 or younger, but its prevalence increases with age, affecting about 1% of the population aged 60 and older. The disease shows a higher incidence in men than in women, with a 1.5:1 male-to-female ratio.

3.2 Vascular Parkinsonism

Out of the total cases of parkinsonism, vascular parkinsonism is responsible for 2.5% to 5% of these cases. The Rotterdam study reported that 5% of participants had parkinsonian features due to cerebrovascular disease. Chang et al conducted a clinical cohort that revealed that out of the total patients with parkinsonism, 4.4% had been diagnosed based on imaging studies and response to levodopa.

3.3 Drug-Induced Parkinsonism

According to a community-based survey, drug-induced parkinsonism has a prevalence rate of 2.7%, whereas a population-based study suggested a prevalence rate of 1.7%. The incidence of drug-induced parkinsonism also increases with age, with the majority occurring in individuals aged between 60 and 80.

4 Etiology

Over the past century, our understanding of the etiology of PD has evolved immensely. In 1919, it was first recognized that loss of pigmentation in the substantia nigra of the midbrain is a feature of the post-mortem brain examination of patients with PD. In the 1950s, it was further understood that the pigmented neurons that are lost in the substantia nigra are dopaminergic, and it is the loss of dopamine in subcortical motor circuitry that is implicated in the mechanism of the movement disorder in PD.

PD is a disorder of the basal ganglia, which is composed of many other nuclei. The striatum receives excitatory and inhibitory input from several parts of the cortex. The key pathology is the loss of dopaminergic neurons that lead to the symptoms.

4.1 Histopathology

Loss of dopamine pigment in the substantia nigra is the key event.

Histologically, PD is characterized by neuronal inclusions of alpha-synuclein in neuronal cell bodies (Lewy bodies) and within neuronal cell processes (Lewy neurites). The hallmark of any neurodegenerative disease is selective neuronal loss, and loss in PD is most marked in the *substantia nigra pars compacta.*

5 History and Physical Examination

An earlier feature of PD is tremor, typically unilateral and present at rest, which is usually the reason for seeking help at a neurology clinic. After using the hands, such as to pick up a book, the tremor may vanish for some minutes, only to return when the patient is

distracted and resting once again. This is the so-called reemerging tremor that is typical of PD.

Although **tremor** is a prominent and early symptom of PD, it is not always present and is not a necessary feature for diagnosis.

Slowness, or **bradykinesia**, on the other hand, is a core feature of PD. Patients will notice it takes them longer to do simple tasks, their walking is slower, and their ability to respond to threats is compromised. In the clinic, patients demonstrate an inability to tap their index finger and thumb rapidly, tap their foot rhythmically on the floor, or walk steadily.

Rigidity is the third prominent feature of the examination. Patients appear stiff and find it difficult to rise out of a chair without support. While walking, there is reduced arm swing, more so on one side than the other, as PD typically is asymmetric at the onset. Checking muscle tone, lead pipe, and cogwheel rigidity can be appreciated.

A combination of bradykinesia and rigidity leads to some other characteristic features of PD, such as micrographia.

The fourth prominent feature of PD is gait disturbance, although this is typically a late manifestation. Flexed posture, reduced arm swing, festination, march-a-petits- pas, camptocormia, retropulsion, and turning en bloc are popular terms to describe the gait in PD. In advanced PD, patients will have trouble rising from a chair without support, they take small, slow steps, they are unable to stop themselves from falling if pushed lightly, they cannot turn around without taking several small steps, and they tend to freeze when faced with certain stimuli such as a doorframe or a passer-by.

Autonomic symptoms are common in PD. Besides orthostatic hypotension, constipation, difficulty swallowing, urinary retention, and erectile dysfunction are common. Often, these symptoms do not improve with treatment.

Depression is also very common in PD. As the disease progresses, dementia with significant loss of cognitive function is common.

6 Treatment / Management

The usual treatment for Parkinson disease involves medications that help manage the symptoms. Anti-parkinsonian drugs are the mainstay symptomatic treatment for parkinsonism, exhibiting varied response intensities and durations depending on the underlying cause. Among the various etiologies, Parkinson disease is the most responsive to treatment.

A multidisciplinary approach to the management of PD is essential. Patients do much better when a structured physical therapy program geared to PD is employed; they can be taught to improve their balance and gait, improve their stability, and maintain an active life. Some unique features of this movement disorder have been exploited to advantage; patients do well with music therapy in physical fitness programs, cycling, and boxing. Patients who cannot walk may find themselves able to dance. Depression, carer fatigue, constipation, REM sleep disorder, paranoia, and psychosis are often seen. They can be side effects of the medication or part of the primary disease, and all need to be addressed.

Regarding medications for Parkinson Disease management, the main drug is **levodopa-carbidopa**. Dopamine itself cannot pass through the blood-brain barrier. However, **levodopa**, an amino acid, can cross this barrier and is metabolized to form dopamine, compensating for dopamine deficiency in Parkinson disease. A peripheral dopa decarboxylase inhibitor, known as **carbidopa**, is coadministered with levodopa to enhance its therapeutic effects. Small doses of combined carbidopa-levodopa, such as 25/100 mg half tablet, are typically administered 2 or 3 times daily with meals. Common adverse effects include nausea, dizziness, and somnolence.

Despite hopes for disease-modifying effects, recent studies have shown that levodopa

does not modify the degeneration process in Parkinson disease, confirming its role as a symptomatic treatment rather than a cure.

7 Prognosis and Complications

Parkinsonism prognosis is highly dependent on the cause and its potential for reversibility, and some other prognostic factors, like the age of onset of symptoms. Late-onset Parkinson disease may have a faster progression rate and earlier cognitive dysfunction. On average, the disease has a duration of 10 years. Individuals have a shortened life expectancy. Early initiation of therapy can help to increase life expectancy. Other causes of parkinsonism also have a quicker onset and progression.

Parkinsonism presents with various complications, including late-onset dementia, autonomic dysfunction such as constipation, urinary incontinence, sexual dysfunction, and diaphoresis, mood disorders such as depression, hallucinations, and psychosis, and sleep disorders such as insomnia and restless leg syndrome. In addition, treatment with high doses of levodopa can lead to the development of dyskinesia characterized by involuntary twitching and head shaking.