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NEURODEGENERATIVE DISEASES : PARKINSON'S

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Abstract:Parkinson's disease (PD) is a gradual and relentless disorder impacting the nervous system. Its onset is subtle, often marked by a barely perceptible tremor in a single hand. Beyond tremors, PD manifests as stiffness and a gradual decline in movement speed.

In the early stages, facial expressions become muted, and arm swing diminishes during walking. Speech may soften or slur. As PD progresses, symptoms intensify, affecting daily life.

While no cure exists, medications can significantly alleviate symptoms. In select cases, surgical interventions targeting specific brain regions offer hope for symptom management.

Keywords: Parkinson's disease, Neurodegenerative disorder, Motor symptoms, Genetic factors, Parkinsonism, Levodopa, Symptomatic treatments, Medical therapies.

Introduction:

Parkinson's disease (PD), also referred to simply as Parkinson's, is a chronic progressive condition affecting the central nervous system, impacting both motor and non-motor functions. Its symptoms typically develop gradually, with non-motor manifestations becoming more prevalent as the disease advances. Early signs include tremors, muscle stiffness, slowed movement, and difficulty walking. Cognitive, behavioral, sleep, and sensory issues can also arise. Parkinson's disease dementia is common in later stages.

The motor symptoms stem from the degeneration of nerve cells in the substantia nigra, a part of the midbrain responsible for supplying dopamine to the basal ganglia. The exact cause of this cell loss is not fully understood but involves the accumulation of alpha-synuclein protein into Lewy bodies within neurons. The primary motor symptoms collectively are known as parkinsonism. Genetic and environmental factors contribute to the disease, with a higher risk observed among those with affected family members and exposure to certain environmental agents like pesticides or head injuries.

Diagnosis of Parkinson's relies primarily on motor-related symptoms, typically affecting individuals over 60 years old, with about one percent affected. Early-onset PD refers to cases occurring in those younger than 50. The average life expectancy after diagnosis ranges from 7 to 15 years. While there is no known cure, treatment aims to manage symptoms. Initial therapies often include medications like L-DOPA, MAO-B inhibitors, or dopamine agonists.

However, these can become less effective over time and may cause involuntary movements. Certain diets and rehabilitative therapies can also improve symptoms. Surgical interventions, such as deep brain stimulation using microelectrodes, may be considered for severe motor symptoms unresponsive to medication. Evidence supporting treatments for non-motor symptoms like sleep disturbances or emotional issues is less robust.

The disease is named after Dr. James Parkinson, who first described it in detail in 1817 in "An Essay on the Shaking Palsy." Public awareness efforts include World Parkinson's Day, symbolized by the red tulip to raise awareness about Parkinson's disease.

History:

James Parkinson first described Parkinson's disease as a neurological syndrome in 1817, although earlier references to Parkinsonism can be found in historical accounts. For instance, Sylvius de la Boë mentioned rest tremor, and Sauvages described festination in the 17th and 18th centuries respectively.
Traditional Indian texts dating back to around 1000 BC and ancient Chinese sources also contain descriptions resembling Parkinson's disease. In concise language, Parkinson depicted the clinical features by reporting on six case sketches, including observations of patients in London streets and from a distance.

Involuntary tremulous motion, with lessened muscular power, in parts not in action and even when supported; with a propensity to bend the trunk forward, and to pass from a walking to a running pace: the senses and intellects being uninjured.

Over 50 years after James Parkinson's initial description, Jean-Martin Charcot provided more detailed insights into Parkinson's disease through his teaching at the Salpêtrière. Charcot and his students categorized the disease into two main types: tremorous and rigid/akinetic. They extensively described associated symptoms such as joint changes, dysautonomia, and pain. Charcot was also responsible for introducing the term "Parkinson's disease," preferring it over earlier terms like paralysis agitans, as he recognized that patients with this condition do not necessarily exhibit marked weakness or tremors. Long before rigidity develops, patients have significant difficulty performing ordinary activities: this problem relates to another cause. In some of the various patients I showed you, you can easily recognize how difficult it is for them to do things even though rigidity or tremor is not the limiting feature. Instead, even a cursory exam demonstrates that their problem relates more to slowness in the execution of movement rather than to real weakness. Despite tremors, a patient is still able to do most things, but he performs them with remarkable slowness. Between the thought and the action, there is a considerable time lapse. One would think neural activity can only be affected after remarkable effort.

In London, William Gowers made significant contributions to the understanding of Parkinson's disease demographics and clinical features in the late 1800s. Drawing from his experience with 80 patients, Gowers noted a slight male predominance and studied characteristic joint deformities. He vividly described Parkinsonian tremors using memorable similes in his writing.

The movement of the fingers at the metacarpal-phalangeal joints is similar to that by which Orientals beat their small drums.

Subsequent clinical descriptions and pathological studies of Parkinson's disease were largely advanced by the French neurologic school. Richer and Meige (1895) provided detailed accounts of the progressive stages of Parkinsonian disability, with Richer producing important visual representations of the disease. Babinski (1921) commented on the unusual motor fluctuations intrinsic to Parkinson's disease. Brissaud proposed substantia nigra damage as the anatomical locus of Parkinson's disease, which was further explored by Trétiakoff (1921), Brissaud (1925), and Foix and Nicolesco (1925) through midbrain pathology studies.

The most comprehensive pathological analysis of Parkinson's disease, including brain stem lesions, was conducted by Greenfield and Bosanquet in 1953.
A key milestone in understanding disease progression came with Hoehn and Yahr's 1967 article, which introduced a widely used staging system based on the development of bilateral symptoms and postural reflex impairment. This staging system remains fundamental in assessing the clinical significance of Parkinson's disease.

Symptoms

The four primary symptoms of Parkinson's disease (PD) are as follows:

- **Tremor**: Tremor typically starts in a hand but can affect a foot or jaw initially. The tremor associated with PD has a distinctive rhythmic back-and- forth motion, often resembling a "pill- rolling" movement involving the thumb and forefinger. This tremor is most noticeable when the hand is at rest or during times of stress, and it tends to disappear during sleep or improve with purposeful movement.
- **Rigidity**: Muscle stiffness or resistance to movement is common in PD. The muscles remain continuously tense and contracted, causing aches and stiffness. When someone tries to move the affected individual's arm, it moves in a ratchet-like or jerky manner, known as "cogwheel" rigidity.
- **Bradykinesia**: This symptom involves a slowing down of spontaneous and automatic movements, which can be particularly frustrating as it makes simple tasks more challenging. Routine movements that were once performed quickly, such as washing or dressing, may take much longer to complete. Additionally, there is often a decrease in facial expressions.
- **Postural instability**: PD can cause impaired balance and changes in. These four primary symptoms—tremor, rigidity, bradykinesia, and postural instability—are hallmark features of Parkinson's disease and can significantly impact daily activities and quality of life for individuals with the condition.

Parkinson's disease (PD) manifests differently in each individual, with varying rates of progression and specific symptoms. Symptoms typically begin on one side of the body before eventually affecting both sides, though often with less severity on one side. Early signs of PD can be subtle and develop gradually. Individuals may experience mild tremors, difficulty rising from a chair, or a slower completion of activities compared to before. Muscle stiffness and reduced movement, accompanied by a lack of facial expression (referred to as a "masked face"), may also be observed. Speech may become softer or hesitant, and handwriting may appear cramped or small. This early phase can last for a significant period before more recognizable motor symptoms emerge.

As PD advances, symptoms may interfere more prominently with daily activities. Tasks like holding utensils steady or reading a newspaper may become challenging due to tremors. Individuals with PD often develop a distinct walking pattern characterized by leaning forward, taking quick steps (festination), and reduced arm swing. They may struggle to initiate movement (start hesitation) and experience sudden stops while walking (freezing). These progressive motor symptoms can significantly impact mobility and daily function as the disease advances.

Classification

PD can be categorized within broader groups of Parkinsonian syndromes that encompass a range of related conditions. It is classified as one of the Lewy body diseases, characterized by the presence of abnormal deposits of alpha-synuclein protein in the brain. Other synucleinopathies in this group include dementia with Lewy bodies, multiple system atrophy, and several other rare disorders. It's important to note that certain rare genetic forms of Parkinson's disease do not exhibit alpha- synuclein aggregation, highlighting the complexity and diversity within the spectrum of this disease.

Pathophysiology

The pathophysiology of Parkinson's disease involves the degeneration of dopaminergic neurons due

to underlying changes in biological activity within the brain. Several proposed mechanisms contribute to neuronal death in Parkinson's disease, although not all are fully understood. Five majormechanisms include:

- Protein Aggregation in Lewy Bodies: One of the primary proposed causes of neuronal death is the aggregation of proteins, particularly alpha-synuclein, which accumulates and forms insoluble aggregates known as Lewy bodies within neurons. While traditionally thought to directly cause cell death, recent studies suggest that Lewy bodies may lead to other detrimental effects that contribute to neuronal demise.
- Disruption of Autophagy: Autophagy, the process by which cells remove damaged or dysfunctional components, may be impaired in Parkinson's disease. Dysfunction in autophagy can lead to the accumulation of abnormal proteins and contribute to neuronal death.
- Changes in Cell Metabolism or Mitochondrial Function: Alterations in cellular metabolism and mitochondrial dysfunction are implicated in Parkinson's disease. Mitochondrial dysfunction can lead to increased oxidative stress and impaired energy production, which contribute to neuronal damage and death.
- Neuroinflammation: Chronic inflammation in the brain, involving microglia and other immune cells, plays a role in the pathogenesis of Parkinson's disease. Excessive neuroinflammation contributes to neuronal injury and degeneration.
- Blood-Brain Barrier (BBB) Breakdown: Dysfunction of the blood-brain barrier, leading to increased vascular permeability and leakage, may allow harmful substances to enter the brain and contribute to neurodegeneration.

Alpha-synuclein plays a central role in these mechanisms. Increased presence of alpha- synuclein leads to the formation of Lewy bodies, which is a pathological hallmark of Parkinson's disease. Alpha-synuclein aggregation may disrupt DNA repair processes, leading to increased DNA damage and neuronal death. Alpha- synuclein aggregates in the cytoplasm, forming Lewy bodies, which reduces its nuclear levels and impairs DNA repair mechanisms. This accumulation of DNA damage and subsequent neuronal death contributes to the progression of Parkinson's disease.Understanding these underlying mechanisms is crucial for developing targeted therapies that can potentially slow or halt the progression of Parkinson's disease by addressing these pathological processes.

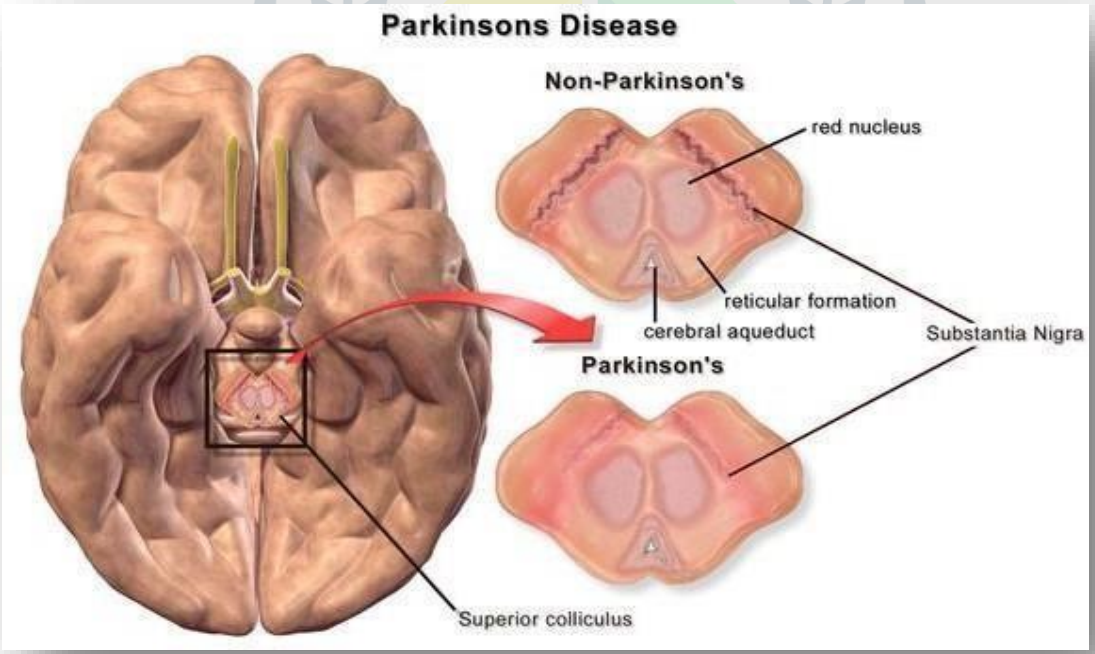

Fig. A brain without and with Parkinson's Disease compared in Substantia Nigra

Treatment

Parkinson's disease (PD) is a complex neurodegenerative condition characterized by a range of motor and non-motor symptoms that necessitate personalized treatment strategies. Effective clinical trials aiming to establish evidence-based outcomes must carefully select participant groups and employ validated, objective assessment tools to evaluate therapeutic impacts.

Although multiple clinical rating scales and tools have been used to assess therapy responses, the Unified Parkinson's Disease Rating Scale (UPDRS) is commonly employed as the primary measure in many trials.

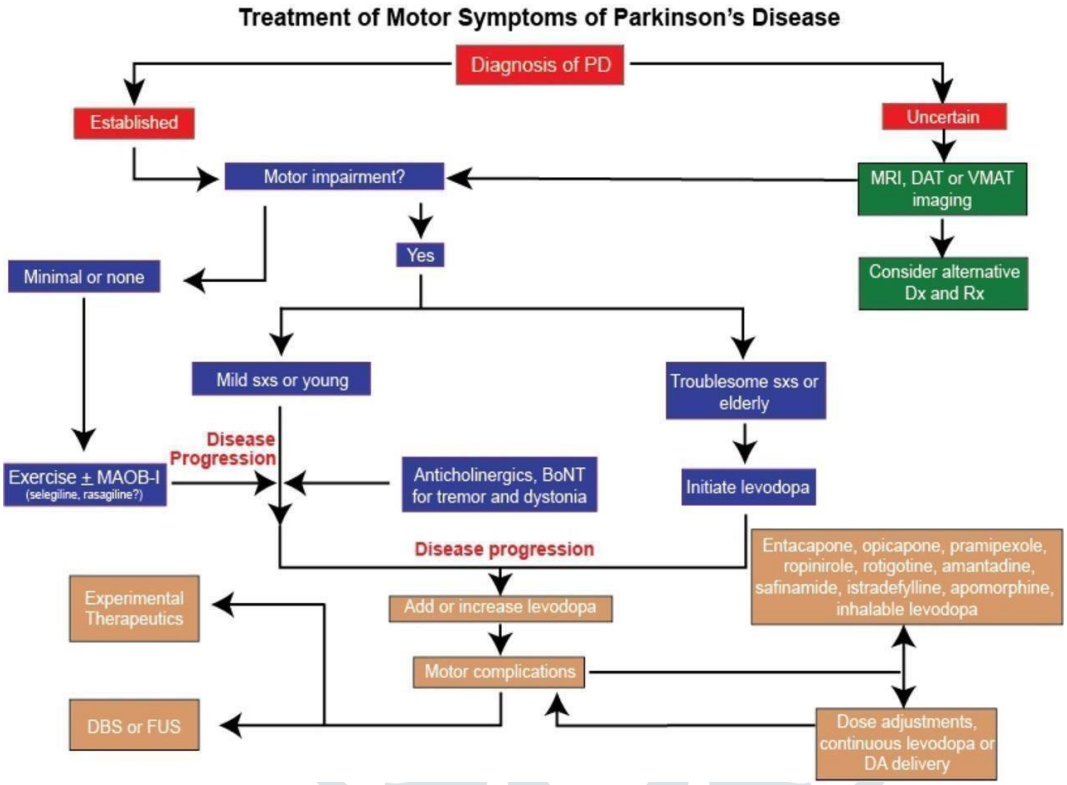

Fig Algorithm for the treatment of motor symptoms of PD. DBS, deep brain stimulation; MAOB, monoamine-oxidase type B inhibitor; PD,

Neuroprotective or disease-modifying therapies

Recognizing the diverse rates of disease progression in Parkinson's disease (PD) highlights the clinical and pathological variability of the condition. With a deeper understanding of PD's causes, there's growing interest in exploring neuroprotective interventions that could potentially alter disease progression, especially if administered early, possibly during the prodromal phase. However, efforts to develop disease-modifying therapies through double-blind placebo- controlled trials have been disappointing so far. The initial trial, DATATOP (Deprenyl and Tocopherol Antioxidative Therapy of Parkinsonism), randomized patients with early PD to receive selegiline (a selective monoamine oxidase B inhibitor), tocopherol (vitamin E), or both until they needed levodopa due to worsening disability. While the selegiline group experienced delayed progression, the study's interpretation was complicated by selegiline's mild symptomatic and antidepressant effects, along with potential impacts from its amphetamine metabolites. Another monoamine oxidase B inhibitor, rasagiline, showed modest symptomatic benefit, but its impact on disease progression remains uncertain.

In the ADAGIO trial (Attenuation of Disease Progression with Azilect Given Once-Daily), investigating rasagiline's disease-modifying potential, the 1 mg dose group exhibited improvement in total UPDRS score and slower progression compared to placebo over 9 months, but no benefit was observed with the 2 mg dose. Due to its symptomatic effects and lack of long-term disease- modifying benefits, rasagiline is not recommended as a disease-modifying treatment.

Developing neuroprotective strategies has been challenging, partly due to the absence of reliable progression biomarkers and an incomplete understanding of PD's pathogenesis. Notable advancements in potential disease-modifying therapies include monoclonal antibodies targeting α- synuclein to reduce toxic accumulation and spread. Other strategies involve immunization against synuclein, anti- aggregation drugs, and specific Abelson (c- Abl) kinase inhibitors like Nilotinib and K0706, aimed at enhancing clearance. Despite these promising avenues, the history of unsuccessful neuroprotective trials suggests caution regarding expectations for imminent approval of safe and effective disease-modifying drugs. Additionally, investigations are underway into glucagon-like peptide 1 receptor agonists and modifiers targeting specific PD-related genes like GBA or LRRK2 (e.g., ambroxol hydrochloride, DNL201, DNL151) within genetically defined parkinsonian populations**.**

Symptomatic treatment of motor symptomsLevodopa

The majority of Parkinson's disease (PD) patients typically require levodopa therapy within two years of symptom onset. Levodopa, the most effective PD treatment, is usually combined with carbidopa or benserazide—aromatic acid decarboxylase inhibitors—to preventperipheral metabolism and reduce nausea risk. Increasing the carbidopa-to-levodopa ratio beyond the standard 1:4 has been shown to extend on-time periods without dyskinesia and reduce off-time.
The reliable global effectiveness of levodopa often confirms a positive therapeutic response and aids PD diagnosis. However, levodopa can cause adverse effects such as nausea, vomiting, orthostatic hypotension, sedation, confusion, sleep issues, hallucinations, and dyskinesias. Dyskinesias, including peak-dose chorea or stereotypy and wearing-off dystonia, are common—with about half of patients experiencing wearing-off and a third developing dyskinesias within two years of starting levodopa. To accelerate levodopa's therapeutic benefits, taking it on an empty stomach (if tolerated), reducing protein intake, or crushing the tablet and mixing it with a carbonated drink can shorten the time to effect.

Concerns about levodopa-related motor complications often deter patients and physicians from starting therapy, particularly in young-onset PD cases prone to early motor fluctuations and dyskinesias. However, delaying levodopa initiation, driven by 'levodopa phobia,' needlessly postpones effective relief of PD motor symptoms. Importantly, there's no evidence that levodopa accelerates disease progression or delays dyskinesia onset when treatment is delayed. Studies like the earlier versus later L-dopa trial found no evidence of levodopa toxicity, although higher doses correlated with increased dyskinesia risk. For patients experiencing short-duration levodopa responses, splitting the total daily dose can help smooth fluctuations and prevent wearing-off symptoms. Additionally, blocking dopamine metabolism with MAOIs or COMT inhibitors, adding dopamine agonists, or using extended-release amantadine can enhance each dose's benefit. Novel levodopa formulations aim to avoid complications— like carbidopa/levodopa extended-release capsules (IPX066) and continuous intrajejunal levodopa-carbidopa gel infusion for motor fluctuation management.

Another approach, approved by the FDA in 2018, is inhalable levodopa powder for 'off' period rescue without carbidopa. This drug requires active inhalation and may cause a cough but offers rapid symptom reversal within 10–30 minutes. Although promising, the therapy's efficacy and tolerability should be carefully considered, especially regarding potential adverse effects like cutaneous nodules with subcutaneous delivery.

Case Study

Muhammad Ali, the legendary boxer, was diagnosed with Parkinson's disease in 1984, three years after he retired from boxing. His diagnosis came at the age of 42, and he eventually passed away in 2016 at the age of 74. Parkinson's disease significantly affected Ali's motor functions, speech, and overall quality of life in his later

years.New evidence from physicians who assessed Muhammad Ali over 20 years indicates that he developed idiopathic Parkinson's disease at an early age.

In a viewpoint published in JAMA Neurology, Michael Okun, MD, from the University of Florida in Gainesville, and colleagues reported that Ali had young-onset tremor-dominant idiopathic Parkinson's disease based on extensive clinical and cinematic monitoring.The authors noted that Ali's symptoms followed a prolonged, progressive course and showed responsiveness to dopamine therapy."This viewpoint marks the first occasion where a group of physicians, who have consistently evaluated him over the years with permission from the family, have officially spoken about his condition," Okun"

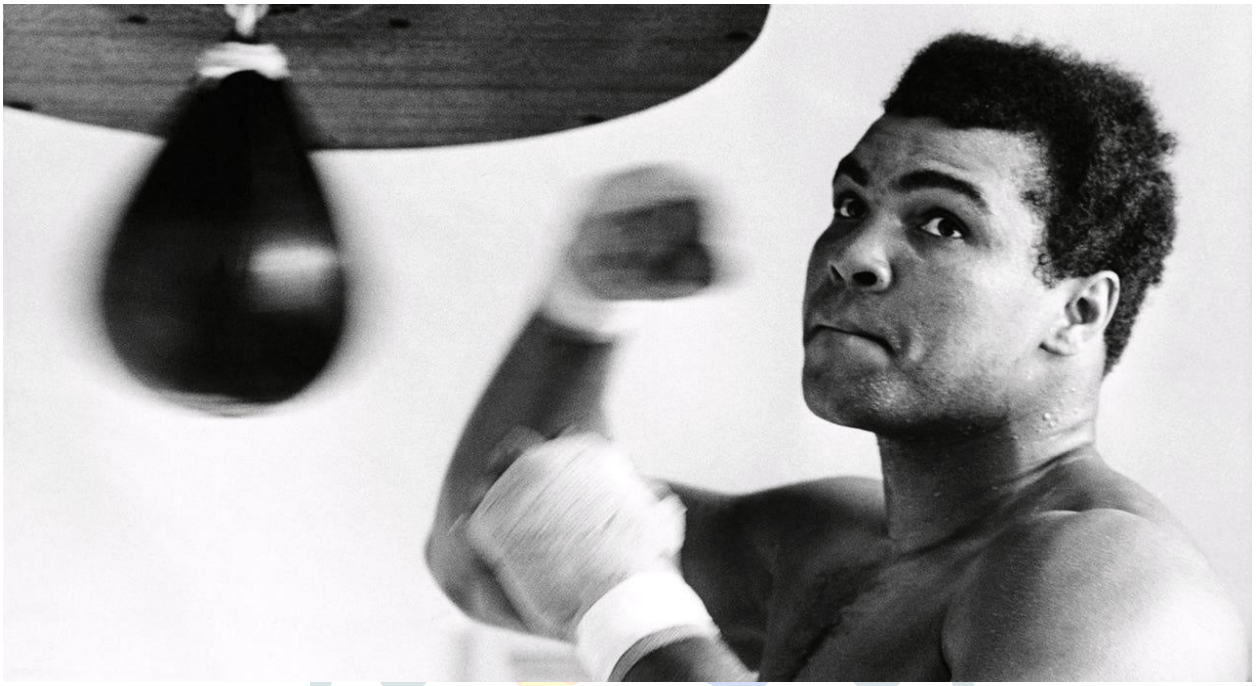

Fig. The Great Muhammad Ali

Okun informed MedPage Today. "Ali holds significant historical importance, and accurately documenting his Parkinson's disease symptoms and disease progression is crucial."

"There remains considerable uncertainty regarding the extent to which Parkinson's disease versus repetitive head trauma contributed to Muhammad Ali's progressive tremor and cognitive decline," he added.

"Over more than thirty years, Muhammad Ali exhibited a progressive, asymmetric, dopamine-responsive resting tremor alongside other characteristic features, strongly indicative of idiopathic Parkinson's disease," Okun emphasized. "Post-traumatic syndromes featuring tremor present differently."

Okun and colleagues highlighted Ali's symptoms in a video depicting his lighting of the 1996 Olympic torch. "Ali displayed a classic left-arm rest tremor associated with Parkinson's disease, which notably diminished as he raised his left hand to steady his right arm for lighting the torch," they observed.

In the late 1970s, Ali's family members observed slowness in his movements, as noted by Okun and colleagues. Between 1981 and 1984, he underwent several medical evaluations at prominent institutions including the University of California Los Angeles, the Mayo Clinic in Rochester, Minnesota, and Columbia-Presbyterian in New York City. These examinations raised the possibility of diagnoses related to head trauma as well as Parkinson's disease or a 'sian syndrome.

From 1995 until his passing in 2016, Ali primarily received neurological care at Emory University in Atlanta. Okun and co- authors reviewed clinical reports spanning 20 years of in-person visits, testing, and hospitalizations at Emory.

"Muhammad Ali experienced a chronic and progressive disease course from his late 30s until his death at age

74," they wrote. "He exhibited symptoms such as fatigue, reduced voice volume (hypophonia), slow movement (bradykinesia), and a mask-like facial expression, along with many other visible motor symptoms characteristic of Parkinson's disease. Notably, he showed clear responsiveness to levodopa, as evidenced by examinations in the early 1980s, a feature typically absent following traumatic brain injury."

According to Okun and colleagues, Ali underwent a fluorodeoxyglucose (FDG) PET scan at Emory University in 1997, which revealed progressive bilateral striatal hyperactivity. A fluorodopa F 18 PET scan conducted in 1998 showed classic low striatal uptake. The authors noted that both these studies supported a diagnosis of Parkinson's disease rather than traumatic brain injury.

During this time, dopamine transporter scanning for distinguishing parkinsonism from essential tremor was not yet available. MRI findings showed brainstem atrophy, enlargement of the third ventricle, and a cavum septum pellucidum.

"Over many years, Ali's facial expressions became increasingly masked, his speech became quieter (hypophonic), and he developed the typical late-stage symptoms of idiopathic Parkinson's disease, including a stooped posture, shuffling gait, postural instability, and frequent falls," observed Okun and colleagues.

Polysomnography confirmed that Ali had rapid eye movement (REM) sleep behavior disorder, and his weight gradually decreased. Serial neuropsychological assessments demonstrated progressive frontal and memory impairments.

The physicians noted, "Ali experienced mild occasional depression but generally remained positive and accepted his diagnosis, despite knowing it was a chronic and progressive condition."

Muhammad Ali passed away from sepsis on June 3, 2016. Despite discussions about an autopsy, Ali declined for religious reasons. "Due to the absence of a definitive tissue diagnosis, we rely on detailed clinical observations and sequential PET imaging studies to comprehend Ali's medical condition. A 34-year chronic and progressive course featuring an asymmetric levodopa-responsive resting tremor, along with other classic symptoms, strongly supports a diagnosis of idiopathic Parkinson's disease," stated Okun and colleagues.

"In contrast, post-traumatic tremor is typically temporary and presents as a tremor during posture or movement," they continued. "Furthermore, post-traumatic tremor does not exhibit progressive cogwheel rigidity and bradykinesia, both of which were observed in Ali."

The authors acknowledged that head trauma is a recognized risk factor for developing Parkinson's disease later in life. However, they emphasized that determining a causal link in Ali's case is challenging.

Conclusion

Parkinson's disease is a neurodegenerative condition primarily diagnosed based on its motor symptoms, although nonmotor symptoms are also common. The exact cause is uncertain but likely involves a mix of genetic and environmental factors, with age and sex being significant contributors. Factors linked to higher mortality risk include the severity and rate of progression of parkinsonism, poor response to levodopa, early onset of gait problems, and symmetry of symptoms. These factors can sometimes lead to misdiagnosis of Parkinson 's-plus syndrome as idiopathic Parkinson's disease, highlighting the challenge of accurate differential diagnosis.
While no treatments that slow or stop disease progression currently exist, a range of medical and surgical therapies are available to manage symptoms—both motor and nonmotor—at different stages of the disease. Ongoing research into emerging therapies through clinical trials offers hope for improved treatment options in the future.

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