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Parkinson's Disease- Etiology, Clinical Features, And Its Therapy: A Review

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Abstract

The second most common age-related chronic progressive neurological condition is Parkinson's disease (PD), the first being Alzheimer's disease. Trembling, bradykinesia, muscle rigidity, and impaired gait and posture are the main characteristics of the disease. Motor deficiencies that characterize Parkinson's disease (PD) are due to the gradual degenerations of neurons in substantia nigra pars compacta (SNpc) leading to reduced dopamine levels in striatum. The most widely used treatment for PD are only partial or reversible and are accessible to only marginal group of patients. Since these remedies do not recover the damaged and degenerated dopaminergic neurons, also does not reduce or stop the progression of the disease, the need for more successful treatment is essential. This review provides a summary of the etiology involved in PD, the clinical symptoms, and its treatment.

Keywords: Parkinsonism, Dopamine, Substantia nigra, Parkinson's disease, Neurodegenerative disease.

INTRODUCTION

Parkinson's disease (PD) is an age-related complex idiopathic neurodegenerative condition illustrated by the gradual neuronal death in the substania nigra pars compacta (SNpc) and widespread concentration of an intracellular protein, alpha-synuclein (aSyn).[1] Dopamine deficiency within basal ganglia leads to classic Parkinson's motor symptoms such as bradykinesia, tremor, rigidity, and subsequent body posture instability. Non-motor symptoms associated with PD appear almost a decade earlier, compared to the motor symptoms. Many non-motor clinical features that precipitate in the later phases of PD are troubling symptoms. Typically, pharmacological therapy is at the root of PD treatment however, these symptomatic treatments are of greatest concern for advanced disease due to their various limitations. [2] There is a substantial economic burden associated with the use of medical services under various direct and indirect costs related to the treatment and management of PD. [3]

The scientifically accurate word paralysis agitans has never been as prominent in use as Parkinson's disease. Initially, it was discovered as a pathological entity, its variability makes use of the term Parkinson's syndrome more appropriate rather than Parkinson's disease. [4] The typical symptoms of tremor, rigidity, instability, and bradykinesia find their primary neurological medium in the reduction of dopaminergic neurons in the nigrostriatal pathway, although the pathogenetic mechanism behind this deficiency may differ. [5]

In 1867 the first medical intervention to help patients with PD was done by administrating *Atropa belladonna* extract. Synthesized anticholinergic agents gained widespread use from the late 1940s. They were the major focus of PD treatment before the introduction of L-dopa during the early 1960s. [6]

While the medical and surgical intervention for PD has made tremendous progress, effective disease-modifying therapy is unavailable. [7] Researchers are, however, optimistic that they will be able to identify various potential disease-modifying treatments (DMTs). In this review, we will address the epidemiology of PD, clinical characteristics, pathophysiology, diagnosis, and medical and surgical management of PD. [8]

Epidemiology

Parkinsonian symptoms may occur either from PD's neuropathological condition (idiopathic PD [iPD]) or from other types of Parkinsonism. 90% of the PD cases are found to be sporadic for neuropathologic PD, with no specific etiology; a supplementary of 10% have a genetic cause, and at least eleven separate linkages with six gene mutations were identified. [9]

Secondary forms of Parkinsonism is usually precipitated by medications, sequelae of infections, toxins, or vascular and metabolic disorders in the CNS. There may also be parkinsonian symptoms of certain neurodegenerative diseases, such as Parkinson Plus or atypical Parkinson’s syndromes and progressive supranuclear palsy. [10]

Advancement of age is the major risk factor in PD. Rural lifestyle, exposure to pesticides and herbicides, well-water consumption, and usage of various solvents at work are some risk factors seen with PD progression. [11]

The epidemiological data on India's PD cases is non-homogenous and small. Razdan et Al. showcased an incidence rate of 14.1 PD cases/100,000 individuals among a total population of 63,645 at Kashmir, India. An incidence rate of 247/100,000 in individuals over the age of 60 years was found. [12] Bangalore in southern India recorded a low incidence of 27/100.000 and 16.1/100,000 was recorded in rural Bengal in eastern India. The high incidence rate of 328.3/100,00 amongst a population of 14,010 Parsees (an ethnoreligious group) living in various colonies in Mumbai in the western part of India. This was reported by Bharucha et al. [13-15]

With advancing ages, the frequency, and prevalence of PD rise in 1% of people over 65 years old. Early-onset Parkinson's disease (EOPD) is identified using the onset of parkinsonism characteristics before 40 years of age. 3-5% of all PD cases are accounted for EOPD. It is categorized into the 'juvenile' (pre-21 years of age) and the 'young-onset' PD (YOPD, 21-40 years of age). In most populations, PD is twice as common in men as in women. This is explained by a protective action that is found to be exhibited by the female sex hormones. This male predominance could be attributed to the existence of gender-based genetic mechanisms and/or gender-specific differences in exposure to various environmental risk factors. [16]

Clinical Characteristics of PD

Parkinson’s Disease is a gradual disorder that appears at an average age 55 and the precedence increases with age from 20/100,000 at age 55, this precedence dramatically increases to 120/100,000 at age 70. While levodopa has improved significantly the quality of life of PD patients, the overall population of these patients continues to demonstrate a decrease in longevity. After 5-10 years since the incidence of the disorder in patients, they display

significant motor dysfunction even when treated expertly with the symptomatic medication that is available. [17]

Any disorder which shows striatal DA deficiency or striatal injuries can lead to parkinsonism. It is a syndrome which is accompanied by tremors at rest, rigidity, slowness and/or absence of postural instability, freezing, voluntary movement. [18] Parkinson's Disease is the common cause in a total of 80% of cases that display the symptoms and features of parkinsonism.

A number of cognitive symptoms ranging from isolated memory and thoughts to major dementia often complicate PD. Studies show that more than 50% of PD patients have some type of cognitive disability. Approximately 20% have more cognitive impairment. [19]

PD memory disabilities are generally milder than Alzheimer's. In the PD, it can be difficult for a person to focus, gain new knowledge, and remember names and other details. Although the etiology of PD is not clear, recent studies have shown the role of oxidative stress (OS) in its pathogenesis. OS contributes to lipid, protein, and DNA damage and causes DA-cell degradation in Parkinson's Disease through a sequence of events.

Symptoms of PD

It may take 15-20 years or longer for the incidence of the symptoms of PD and their progression, and it may differ between individuals.

MAJOR SYMPTOMS

Muscle rigidity (muscle rigidity) and shaking and bradykinesia (voluntary movement speed) are the major symptoms seen in patients with PD. Other causes that show the clinical features of PD are antipsychotic side effects, tumours, etc.

Rigidity affects the body's muscles on one or both sides of the body. The involvement of face muscles triggers a fixed or masked face expression and slurred speech. A stooped posture arises, in part, to neck and back muscle rigidity.

In the hands and sometimes in the feet, tremors can develop. Sometimes, they appear in the head, neck, face, and jaw, and it can become worse on one specific side of the body. Stress, tiredness, and emotions worsen tremors.

Bradykinesia is one of Parkinson's disorder's most impairing symptoms. The delayed movement initiation decreased movement and sudden failure to move are some of the characteristic features. It also causes balance problems, leg 'freezes,' walking and/or turning difficulties, and a lack of facial expressions. [20]

MOBILITY PROBLEMS

Automatic movement loss: action or movement requires thinking and working. Mental and physical activities need more effort and are physically draining. [21]

Gait is unnatural: Gait is fast and mixed. It can be characterized by short steps and shuffling like movement.

Mobility fluctuations: The shift in energy levels also has an effect on mobility.

Leg freezing: Later in the course of the disease this issue arises. The person suddenly can not move while walking. [22]

COGNITIVE CHANGES

- Depression: Depression may be a normal occurrence or side-effect of levodopa, or any Parkinson's disease medication of choice. [23]
- Changes in personality: Irritability, suspicion, and lack of motivation are frequently challenging problems.
- Changes in the subconscious: The disease usually does not impair cognitive abilities and does not cause any intellectual changes. [24]

SPEECH AND COMMUNICATION PROBLEMS

- Low volume of speech and monotone voice: The muscles regulating respiration are impaired in Parkinson 's

disorder. This condition affects speaking rhythm, tone and pronunciation rate, and phrase. [26]

- Diminished facial expression: As mentioned earlier, because of loss of muscle control, the face of a person with Parkinson is less versatile and less expressive in nature.
- Reduced use of gestures: Individuals with Parkinson's disorder are not able to interact with their hands and bodies to communicate non-verbally. [27]

PHYSICAL AND FUNCTIONAL PROBLEMS [28][29]

- Minor pains and aches: They include arm or leg soreness because of tremors and/or rigidity or foot cramps.
- Foot and ankle swelling (edema): Decreased leg movement can lead to swelling in various parts of the leg.
- Oily or dry skin scaly (seborrhea): Seborrhea is caused by overactive skin oil glands, especially on the face, forehead, and sides of the nose.
- Itching or burning of the eyes (conjunctivitis): Reduced frequency of eye blinking results in dust and smoke particles and other irritants to remain longer on the eye, causing itching or burning sensation.
- Problems of the eye: Double-sight, distortion and sporadic movement of the eyes are some of the problems that arise.
- Sleep disturbances: Certain issues include vivid hallucinations and/or dreams sleep talking and involuntary jerking of the limb is observed.
- Problems with breathing: Rigidity or extreme slowness (bradykinesia) of the muscles of the thoracic wall prevents lung expansion.
- Swallowing problems (dysphagia): The failure to contract the throat muscles leads to various swallowing problems.
- Drooling: The individual cannot swallow saliva which results in drooling.

SOURCES OF MOTOR IMPAIRMENT

(i) Effect of dopamine:

Parkinson's disease (PD) affects nerve cells in deep brain regions known as the Substantial Nigra and Basal Ganglia, which are a group of nuclei situated at the base of the forebrain. [30] Substantial nigra nerve cells produce the neurotransmitter dopamine, a crucial brain monoamine that relays messages which direct and control the movement of the body. Although DA predominantly works as an inhibitory neurotransmitter and plays a major role in motivation, memory, concentration and most importantly the direction and regulation motor control (physical movement and coordination). In a healthy functioning brain, DA controls the excitability of striatal medium spiny neurons (MSN), also known as spiny projection neurons (SPNs), a major type of cell present in the striatum which influences initiating and regulating movements of the body, limbs, and eyes. In PD, DA-neurons of pars compacta in the basal ganglia, degenerate and the DA levels decrease. Insufficient levels of DA reduce the inhibition of the striatal microcircuits, enabling them to fire excessively. It makes the control of the movements of PD patients difficult and results in tremors, rigidity, and bradykinesia, which are the main characteristics of motor symptoms associated with PD. [31]

(ii) Effect of serotonin:

Besides DA, serotonin (5-HT), another monoamine neurotransmitter, plays a very particularly a major part in many motor and non-motor symptoms '5-HT syndrome', including include tremor, myoclonus, psychosis, rigidity and hyperreflexia, Levodopa-induced dyskinesia, that worsens PD features. [32] A decrease of the level of serotonin in the pre-frontal cortex (PFC) is seen in about 18 weeks in neuro-toxin-induced MPTP induced animal model for PD. [33] Moreover, a reduction in SERT-immunoreactive serotonergic ($SERT^+$) axons in PFC was seen in the brains which decreased the serotonin-immunoreactive (SER-IR) neurons the dorsal raphe (DRN)

and median raphe (MRN) nuclei or lower SERT binding index in PFC regions. [34] In addition, there is an approximate twenty-five percentage loss of serotonin 1A receptor (HT1A) at the MRN which is linked to the severity of resting tremor suggesting that the 5-HT midbrain projections are more relevant to the incidence of PD tremor than the loss of topographical projections by the dopamine neurons in the nigrostriatal pathway. [35][36] In recent years, it has been shown that serotonin turnover in PFC can be of critical importance in the mitochondrial dysfunction of the toxin model of Parkinson's disease. Additionally, several investigations in PD found a strong relationship between the reducing levels of 5-HT and depression. [37]

(iii) Role of acetylcholine:

In many neurological disorders including Parkinson's disease and Alzheimer's disease, acetylcholine (ACh) plays a major part which is understudied. In the cortical subventricular zone (SVZ), a proliferative compartment in the forebrain, there is a cholinergic system of the basal forebrain, prominently known as the nucleus basalis of Meynert (NBM). (38) The nucleus basalis of Meynert is a large source of cholinergic innervation to widespread cortical areas. In patients with Parkinson's disease, Lewy body dementia, Alzheimer's disease, or other types of dementia, different patterns of neuronal loss were found in the cholinergic neurons of NBM. [39] Particularly in the brain tissue, NBM of PD patients with cognitive impairment presence of Lewy bodies and neuronal loss were found. This indicated that the cholinergic system is correlated with cognitive dysfunction observed in the PD. [40]

(iv) Role of GABA/Ca2 + system:

The gamma-aminobutyric acid (GABA) is an inhibitory neurotransmitter that regulates the Calcium influx and Calcium current directly via L-Type Voltage-Gated Calcium Channels by Positive Allosteric Modulators of GABA-A Receptors and, indirectly, through the network of astrocytes. [41] The mechanism of Ca2+/GABA stabilizes both cellular and systems neuronal activities. The Ca2+-buffer system is disrupted in the case of PD, due to mitochondrial dysfunction, which leads to calcium-dependent excitotoxicity which contributes to excitotoxic neuronal damage in the pars compacta in the basal ganglia, whereas the inhibitory GABA receptor activity regulates the Ca2+-buffering system. [42] It has been found that approximately 80% of the newly diagnosed patients with PD have a considerable olfactory impairment, the loss of olfactory acuity, which is due to DA-neuron injury in the olfactory bulbs. [43] The functions of the brainstem and olfactory system of the DA-neurons is controlled by a Glial cell line-derived neurotrophic factor (GDNF), which show a pronounced neuroprotective effect controlled by the GABAergic neurons system (interneurons and striatal neurons). In GABAergic projecting striatal neurons, the neuroprotective effects of GDNF were observed in PD animal models, indicating that the GABA receptor activity regulates the Ca2+-buffering system contributes to the dopamine (DA) neuronal death in PD. [44]

PHARMACOLOGIC MANAGEMENT

The development of disease-modifying therapies that can delay or stop the neurodegenerative process is the main objective of research that is conducted on PD. However, there is no conclusive disease-modification therapy available to accomplish this objective. [45]

Dopaminergic therapy

As the patients suffering from PD have cognitive disorders it is recommended by the American Academy of Neurology (AAN) that one of the below drug therapies be initiated. The treatment for motor diagnoses would include Levodopa /carbidopa, ergot-derived dopamine agonists and non-ergot-derived dopamine agonists, mono-oxidase-B (MAO-B), inhibitors of injectable dopamine agonist (apomorphine) inhibitors and

inhibitors of the N-methyl - D-aspartate (NMDA) antagonists, catechol-O-methyltransferase (COMT) antagonists and also parasympatholytics. During the later phases of the progressive disorder, the delivery of pharmaceutical agents is possible through alternate routes like subcutaneous injections, transdermal patches, etc.

Bradykinesia and rigidity are two of the most significant symptoms of PD. Dopamine therapy is highly effective for the slowness of movement and rigidity, but irreversible and reversible inhibitors of MAO-B monoamine. Dopamine and levodopa stimulants lead to the reduction of the progression of the disorder along with that it also reduces the inabilities caused by the disorder. Tremor responds to the use of parasympatholytic agents including trihexyphenidyl but has an ineffective and systematic response to dopamine replacement therapy. [46]

Dopamine agonists

The dopamine stimulants or agonists, precisely target the D2 receptor family. The first members of this group of agents were Ergot derived dopamine agonists. These ergot derived agents raised a major concern about cardiac and pulmonary health. Non-ergot derived dopamine agents, for example, pramipexole, rotigotine, apomorphine, ropinirole are currently being used. Dopamine agonists produce fewer pulsating dopamine receptor stimulation than levodopa, thereby reducing the possibility of motor problems when used as initial monotherapy.

Apomorphine has both D1 and D2 receptor activity as well as the potency of levodopa. The continuous subcutaneous infusion of apomorphine decreases the inconsistency of the motor activity and dyskinesia caused by levodopa.

The receptor activity of apomorphine is on both D1 and D2 receptors of the dopamine family of receptors. Apomorphine also has the same effectiveness as levodopa. The continuous subcutaneous infusion of apomorphine reduces motor activity inconsistency and levodopa-induced slowness in moments. The transdermal patch formulation enables newer dopamine agonists like rotigotine, to be delivered continuously. [47]

MAO-B inhibitors

MAO-B inhibition contributes to a rise in synaptic dopamine production and symptomatic effectiveness. Since the 1970s, levodopa shown to be effective when being used as an adjunct along with selegiline which is MAO-B inhibitor of irreversible type. These properties were also shown by selegiline.

A common addition therapy for motor fluctuation patients is Rasagiline, an irreversible inhibitor of monoamine oxidase-B. A retrospective cohort study conducted over the span of three years, to determine the relationship between the risk factor and the disease has tested the effectiveness of MAO-B inhibitors in PD and has shown similar effectiveness in regulating motor symptoms in PD patients receiving optimized clinical therapy. A noticeable drop in L-dopa demand and a lower incidence of dyskinesia has been associated with this form of therapy.

Safinamide is an antiglutaminergic reversible MAO-B inhibitor. It is most commonly used as an add-on treatment for PD. Safinamide improves muscle performance in advanced-stage PD and enhances the quality of life by increasing control over motor fluctuations. In a new randomized clinical control trial, when safinamide is used as an additive to L-dopa, decrease in dyskinesias-induced weakness and its frequency is reported. [48]

Catechol-O-methyl transferase (COMT) inhibitors

Current formulations of L-dopa contain carbidopa/benserazide to hinder dopamine metabolism and thus enhance the bioavailability of previous medicinal formulations. It transfers levodopa to an alternative pathway that involves COMT in the peripheral catecholamine metabolism by methylating these catecholamines. COMT pathway inhibition also improves bioavailability and the half-life of levodopa. COMT inhibitors can help reduce the

fluctuation of motor symptoms that many patients being treated with carbidopa/levodopa experience. Triple treatment with levodopa/carbidopa/COMT inhibitors significantly increases “on” episodes, reduces “wearing-off” episodes and improves the quality of life substantially. Entacapone and Opicapone are two of the most used peripheral catecholamine inhibitors. [50]

Non-Dopaminergic Pharmacological Targets

The late-stage PD motor and non-motor symptoms respond badly to dopamine therapy. Various non-dopamine neurotransmitters, for example, Glutamate, Norepinephrine, Ach, Serotonin can trigger other problems. The symptoms which require treatment with the non-dopaminergic medical products include movement instabilities, levodopa-induced slowing of body moments gait and other gait disorders, postural instability and frequent falling, swallowing and speech difficulties and other similar manifestations of the disorder.

Insufficiency of acetylcholine induces depression, gastric disorders and frequent falls due to the loss of parasympathomimetic neurons. Anti-cholinesterase agents are used for the therapy of such symptoms. The trial of donepezil conducted for the treatment of the frequent falls is linked to the presence of an irregular parasympathomimetic system in PD patients. Rivastigmine, an acetylcholinesterase inhibitor, is used for PD related dementia. Rivastigmine effectiveness is examined in randomized trials in the treatment of gait disorders and frequent falls.

In PD patients, depression is responsive to all types of antidepressants, however, insufficient evidence is available to support tricyclic antidepressants (TCAs) against serotonergic antidepressants. In clinical trials, the function of norepinephrine agonist agents must be strongly established. All atypical neuroleptics, apart from quetiapine, intensify the parkinsonism disease by blocking D2 striatal receptors. Parkinson's psychotic symptoms respond well to clozapine, an atypical antipsychotic medication. Clozapine's serotonergic role in psychosis is supported by the new substantially positive results, using pimavanserin tartrate, a 5-hydroxytryptamine, (5-HT2A) inverse agonist. It is prominently used therapy for L-dopa-induced psychosis in PD patients.

One of the N-methyl-D-aspartate (NMDA) receptor antagonist utilized aimed at Levodopa-induced dyskinesias and other motor disorders is 1-Adamantylamine. It is commonly known as Amantadine. There are various guidelines that vary on the use of amantadine in the therapy for dyskinesia associated with parkinsonism. Movement Disorders Society's evidence-based study found that Adamantylamine was 'efficacious' in the therapy of dyskinesias, while the American Association of Neurology (AAN) guidelines stated that it was 'possibly efficient'.

Patients with PD are impaired by autonomic dysfunction due to the loss of dopamine-producing neurons occurs by a non-autonomous and autonomous process, especially in the advanced stages of PD. This involves gastrointestinal disorders, central neurotransmitter system dysregulation, urinary disorders, sexual dysfunction, impaired pupillary reflexes, and other such disorders. Pharmacological treatment directed towards the autonomic nervous system involves the use of mineralocorticoid, fludrocortisone, as well as the use of various adrenergic agents, the norepinephrine prodrug (droxidopa) to treat orthostatic hypotension; antimuscarinics to treat urinary dysfunction; and, pro-kinetic drugs to help in improving constipation and L-dopa-induced gastroparesis. [51]

Tyrosine kinase inhibitors

Upregulation in the rates of Abelson (C-Abl gene), a nonreceptor tyrosine kinase, are seen in the patient's brain tissue suffering from PD. Some of the agents that show BBB penetration and inhibit this gene include Radotinib, Imatinib and Nilotinib. Karuppagounder et al., tested the in vivo effectiveness of a new brain-penetrating specific c-Abl kinase inhibitor, in the acute MPTP-induced mouse model of Parkinson's disease and found that nilotinib prevented dopamine neuronal loss and behavioural defects following MPTP mediated intoxication. Nilotinib has more potency which

is an attractive treatment for neurological disorders with decreased c-Abl activation, levels of Parkin substrates, including mitofusins Mfn1 and Mfn2, and also showed significantly reduced neuronal cell death.

Imam et al. tested the effectiveness of INNO-406 (a second-generation Potent and Selective Dual Bcr-Abl/Lyn Tyrosine Kinase Inhibitor) and found that INNO-406 was able to prevent the dopaminergic neuronal degradation in a Neurotoxin-Induced C57 Animal Models of Parkinson Disease. Researchers have shown that c-Abl inhibitors may prevent the loss of dopamine neurons, enhance the motor activity, inhibit phosphorylation of Cyclin-dependent kinase 5, control α-synuclein phosphorylation and reduce the rates of Parkin substrate, including mitofusins Mfn1 and Mfn2. Abelson inhibitor which has the potential to permeate the brain can be employed as a therapeutic agent for treating various neurodegenerative diseases. [52]

Surgical treatment

Deep brain stimulation (DBS) from either of the subthalamic nucleus (STN) or globus pallidus interna (GPi) is a familiar procedure for patients with motor dysfunction. For therapy of tremors, thalamic DBS is a feasible alternative. The average amount of time before DBS is implemented is around 10–13 years after the diagnosis of Parkinson's disease has been identified. Outcomes of the controlled trial with deep brain stimulation in patients with early Parkinson's Disease, also known as the EARLY-STIM trial showed that DBS in the early course of the disorder could boost the patient's condition and multiple secondary outcome measures.

DBS may be reversed and adapted to the progression of the disease. DBS exclusion criteria include the occurrence of dementia, acute psychotic illness, and severe depression. In comparison with the preoperative medical "wearing-off" episode, Bilateral deep brain stimulation of subthalamic nucleus (STN-DBS) increases average Unified Parkinson's Disease Rating Scale-II (UPDRS II) (daily living activities) and UPDRS III (motor) values by 50%–60%. The overall regular L-dopa dose after DBS is lowered by approximately 60% and dyskinesia is reduced by 60–70 %. DBS mortality is less than 0.5% due to the decline in various significant adverse events include intracranial bleeding, etc. [53]

Non-pharmacological treatments available for PD include exercise, education, support group, speech therapy, and a nutritious diet. Literature evidence suggests its early use and implementation during the course of the disease for a slower progression of the disorder. [54][55]

CONCLUSION

Parkinson's disease is one of the most prevalent neurodegenerative disorders affecting the ageing population and is related to increased morbidity or mortality rate. For the optimal management of cases, awareness of the manifestations of the disorder, the various treatment options, and the progression of the disease over the course of time is essential. Economic and emotional implications of patients on the mental and physical health of the families and friends of people suffering from this disorder are severe. Earlier diagnosis of the disease can be helpful to screen susceptible individuals. In addition, some medicines have serious side effects and are costlier to maintain. Scientists recently proposed several interesting and promising new methods for treating this disorder which includes stem cell transplantation and gene therapy. Although, none of these treatments is capable of completely curing PD. Parkinson's disease, a gradually advancing disease, can lead to severe disabilities because of the increased severity of motor and non-motor symptoms which can become resistant to treatment. Current and future research efforts must address the unanswered key factors that lead to the progression of the disease and further factors that impede the disabilities of the disease.

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