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Long-Term Cognitive and Functional Outcomes in Parkinson's Disease: Current Evidence and Emerging Insights

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ABSTRACT

Parkinson's disease (PD) is a progressive neurodegenerative disorder characterized by motor symptoms such as bradykinesia, resting tremor, rigidity, and postural instability as well as a wide spectrum of non-motor manifestations including cognitive impairment, mood disturbances, sleep dysfunction and autonomic abnormalities. One of the most common concomitant diseases in PD is dementia which can be seen as a gradual cognitive decline especially in executive function, attention and visuospatial skills. Functional decline and its progression in patients are variable depending on various factors such as the age of disease onset, motor type, comorbidities and neurobiological mechanisms such as alpha-synuclein aggregation and the breakdown of cholinergic activity. Emerging neuroimaging and biomarker technologies are being examined to ascertain their role in predicting future patients' responses and directing personalized medical treatments. Apart from the mental activities and medical treatments, physical exercises, occupational therapy and cognitive rehabilitation all help in sustaining patients' independence and mental well-being. Additionally, caregivers are unparalleled in achieving better results for patients. Future research integrating precision medicine, digital health technologies and disease-modifying therapies promises to improve longterm cognitive and functional trajectories in PD.

Keywords: Parkinson's disease, Cognitive impairment, Functional decline, Neurodegeneration, Neurorehabilitation, Biomarkers

1. Introduction

Parkinson's Disease (PD) is regarded as the second most common neurodegenerative disorder caused by aging and the foremost worldwide movement disorder, which was initially referred to as "Shaking Palsy" by James Parkinson in the early 19th century[1]. PD brings about the death of dopaminergic neurons in the substantia nigra pars compacta causing the depletion of striatal dopamine, the motor symptoms being resting tremor, bradykinesia, rigidity and postural instability, which are actually the reflections of such a process. The diagnosis of PD is still

based on motor symptoms; however, the disease brings about non-motor phenomena as well, which can be under cognitive deficits, mood disorders, autonomic dysfunction, sleep disruptions and sensory symptoms[2].

The pathophysiology of PD is not confined to the loss of nigrostriatal dopaminergic neurons but includes extensive involvement across the central and peripheral nervous systems[2]. One of the key neuropathological features of PD is the formation of Lewy bodies and Lewy neurites, cells with proteins abnormally folded mainly made of α-synuclein. This scenario of protein misfolding links PD with other similar conditions, termed synucleinopathies and proposes common pathogenic pathways with other neurodegenerative disorders characterized by protein conformational changes[1].

The clinical picture of PD is very diverse, showing different mixtures and levels of both the motor and non-motor symptoms and the patient's disease will change substantially during the course of the whole disease[2]. Age is the most influential risk factor; however, genetic, environmental and lifestyle factors also play a role in the disease's vulnerability and advancement[1].

2. Overview of Parkinson's Disease

Parkinson's Disease (PD) is an advancing neurodegenerative disease mainly characterized by motor signs, that is, bradykinesia, resting tremor, rigidity and postural instability. These classic motor manifestations are caused by the death of dopamine-producing neurons in the substantia nigra pars compacta and the resulting disordered basal ganglia circuits that control movement. PD is recognized as the second most prevalent neurodegenerative disorder worldwide, affecting almost 1% of the population over the age of 60 and the prevalence of the disease is directly related to age[3].

PD was for a long time seen primarily as a disorder of movement only but nowadays, it is very well recognized as a multisystem disease with a wide variety of non-motor symptoms, some of which can even precede the motor signs by many years. The non-motor manifestations are cognitive decline, depression, anxiety, sleep problems, dysfunction of the autonomic nervous system, loss of smell and digestive disorders. These symptoms have a major impact on the patient's quality of life and are very often not acknowledged in clinical practice, which leads to the delay of the initiation of proper management[4].

The etiology of PD is attributed to a complex interplay of genetic, environmental and aging-related factors. Mutations in a number of genes, including SNCA, LRRK2, PARK2 and PINK1, lead to the development of familial forms, while sporadic PD is associated with the exposure to environmental toxins, oxidative stress, mitochondrial dysfunction and neuroinflammation[3]. Pathologically, PD is characterized by the presence of Lewy bodies, intracellular clusters of alpha-synuclein, which are the major contributors to neuronal dysfunction and death[3,5]. On the other hand, the dispersal of Lewy pathology to the cortex and subcortex is responsible for the involvement of these areas, which in turn, dilutes the motor and cognitive deficits.

In terms of symptoms, the progression of PD is of different types and severity, as some patients are showing tremor dominance, while the others are suffering from postural instability and gait problems, among other symptoms, earlier on. Such differences in the manifestation of the disease are correlated with different rates of disease progression, response to treatment and the likelihood of developing cognitive decline and dementia in the long run[4]. Therefore, timely identification of both types of symptoms, i.e., motor and non-motor and their characterization are important for making proper prognostications, selecting right treatments and thereby, improving long-term outcomes for patients with PD.

3. Cognitive Impairment in Parkinson's Disease

Cognitive impairment is a frequent and clinically relevant non-motor symptom of Parkinson's disease (PD), which impacts patients during all phases of the disorder. Although initial studies were mainly concerned with the motor symptoms, it has now been established that up to 30% of recently diagnosed PD patients have mild cognitive deficits, with the rate of occurrence increasing as the disease progresses, eventually leading to the dementia associated with Parkinson's Disease (PDD) in a large part of the patients[6]. Cognitive dysfunction associated with PD generally impacts various domains such as executive function, attention, visuospatial skills and memory, which encompasses the widespread involvement of cortical along with subcortical networks beyond just the dopaminergic nigrostriatal pathway[6,7].

Besides, executive dysfunction is very much early cognitive deficit and is usually observed through difficulties in planning, problem-solving, multitasking and working memory. These deficits are attributed to the impairment of the frontal-striatal circuitry along with the depletion of dopamine in the prefrontal cortex which hinders the interaction between the basal ganglia and cortical areas[7]. The problem of visuospatial along with executive deficits is more frequent in the case of people with memory loss, which may lead to disability in performing the activities of daily living. Memory loss in PD is usually not as serious as in Alzheimer's but mostly consists of the patient being unable to recall rather than understand, indicating a subcortical type of dysfunction[6].

In the case of cognitive decline, longitudinal studies that monitor patients suffering from PD, disclose a heterogeneous pattern with some patients displaying stable, unchanged cognitive function for several years while others witness a rapid decline resulting in PDD[8]. Amongst various factors that forecast the cognitive impairment course, older age at onset, the severity of motor symptoms and the presence of non-motor symptoms such as hallucinations or depression, as well as certain motor phenotypes like postural instability and gait difficulty are the most significant ones[8]. It is essential to comprehend these predictors, as they determine one's future cognitive status and choose the best interventions accordingly.

In Parkinson's disease, cognitive impairment is considered a result of the triad of alpha-synuclein accumulation, inflammation of the nervous system and insufficient functioning of the neural systems that utilize acetylcholine, which includes the cortex and subcortex. The changes in the brain's structure and the activity in the regions that are engaged in executive and memory function have been substantiated by neuroimaging studies[6,7]. Similarly, the overlapping pathology of Alzheimer's disease, like the formation of amyloid-beta deposits, may also be a reason for cognitive deterioration in some patients which makes the issue of PDD more complex[7].

The detection and assessment of cognitive impairment in PD constitute an integral part of the holistic approach to patient

care. The early detection means that the cognitive rehabilitation techniques, the pharmacological treatments for cholinergic and dopaminergic systems and counseling for the patients and caregivers to help them cope with the situation and use the same quality of life can all be set in motion in no time[6,8]. Therefore, cognitive testing should be made part of the routine clinical assessment in Parkinson's disease just like motor examinations are done.

4. Functional Decline and Activities of Daily Living

Functional Decline, characterized by the progressively impaired ability to perform daily activities, is one of the most noticeable symptoms of Parkinson's Disease (PD) and it heavily connects with both motor and cognitive impairments, thus, it decreases the patients' independence and overall quality of life. Activities of Daily Living (ADLs) which cover basic tasks such as dressing, eating, bathing and mobility as well as instrumental tasks like managing finances, cooking and using transportation, are progressively compromised as the disease advances[9]. Motor symptoms like bradykinesia, rigidity and tremor are indeed the main culprits, but cognitive dysfunction, especially among the elderly, is a great contributor to functional limitations[9,10].

Research has shown that ADLs are often impaired at an early stage, often in the form of pre-diagnostic symptoms or mild disease stages, thus drawing the attention towards the importance of preventive functional assessment[10]. For example, minor trouble in multitasking, sequencing complicated activities or doing household chores may entail the onset of less visible motor disability. These minor deficits are in line with faster functional decline and can be even an early indicator of the patient developing Parkinson's disease dementia[10]. Long-term studies in addition have shown that the decline in functions more or less is not the same for all patients; those with major executive dysfunction or visuospatial impairment suffer more quickly the loss of independence than those with predominantly motor-predominant phenotypes[11].

Interventions that aim at improving functional outcomes in Parkinson's Disease (PD) involve both pharmacological and non-pharmacological methods. The best dopaminergic treatment can reduce the symptoms of the disease and thus indirectly help the patient in performing Activities of Daily Living (ADL). Moreover, the occupational and physical therapy interventions, including task-specific training, exercise programs and environmental modifications, have been established as effective methods in preserving or increasing daily functioning[11]. Cognitive rehabilitation and compensatory tactics, such as structured routines and assistive technologies, are gaining acceptance as integral supplements to the conventional motor-oriented care, especially for the patients with cognitive decline and motor disability[9,11].

To understand the interaction between cognitive and motor deficits as a factor in driving functional decline is vital for patient management in its entirety. Regular assessments of both ADLs and instrumental ADLs are strongly recommended for the physicians as they will be able to schedule timely interventions and care planning according to the patient's needs. Early detection of functional limitations not only honors the independence of the patient but also lightens the caregiver's load and saves healthcare costs in the long run[9,10].

5. The Development of Cognitive and Functional Outcomes Over a Period of Time

The decline of cognitive and functional capacities in Parkinson's Disease (PD) is not the same in all cases. It is highly variable, reflecting the complex interaction of motor, non-motor and neurodegenerative factors. Longitudinal studies show that cognitive defect in PD gradually progresses, starting with very slight executive and attention deficits and possibly leading to Parkinson's Disease Dementia (PDD) in some patients. At the very beginning, executive dysfunction, memory retrieval deficits and visuospatial impairments would appear, while language and praxis disturbances would be more severe and would generally be in the later stages[12]. Cognitive deterioration goes along with functional decline, but the timing of the onset and the speed of progressive decline vary from one individual to the other. The main factor in the performance of the basic activities of daily living (ADLs) is motor impairment; while remaining cognitive deficiencies are a threat to instrumental activities, such as managing money, taking medication on time and moving in complex environments[13]. Results from the research indicate that early loss of executive functions is a great predictor of rapid functional decline, which illustrates the interdependence of cognitive and motor systems in the preservation of independence[12,14]. The course of the heterogeneity of disease progression is affected by different factors, such as age when the disease started, how long it has been, how severe the motor symptoms are and what motor phenotypes they are. For instance, those with postural instability and gait difficulty are quicker to show declines in both mobility and ADL performance than individuals with a tremor-dominant type of Parkinson's[13]. Moreover, coexisting disorders like depression, sleep difficulties and autonomic dysfunction can worsen cognitive and functional decline and make management even more difficult[12].

Longitudinal neuropsychological assessments and functional evaluations have shown that even with optimal dopaminergic therapy, cognitive and functional decline might still continue, thus stressing the necessity for early and multifaceted interventions[14].

6. Progression of Cognitive and Functional Outcomes Over Time

The long-term cognitive and functional outcomes in Parkinson's Disease (PD) are the result of a mixture of demographic, clinical and disease-specific factors. The age at which the disease starts is the main predictor, with older patients being more likely to experience rapid cognitive decline and functional impairment. Equally, longer disease duration and advanced motor stages have been linked to the greater risk of disability and a lesser degree of independence[15].

Patients who experience postural instability as well as having problems with gait are more prone to suffer functional deterioration and dementia compared to patients with tremor-dominant disorder. The existence of non-motor symptoms such as depression, hallucinations and autonomic dysfunction is another factor that predicts poor long-term outcomes by aggravating the state of mind and complicating the daily living activities[16].

Cognitive status at the start of the treatment is another very important predictor of the outcome. Slight executive dysfunction, poor attention and visual-spatial deficits in people with early stages of the disease may often be a sign of their genetic

predisposition to suffer from the loss of cognitive abilities. Moreover, the existence of other diseases such as vascular disease or metabolic disorders can speed up the progression of the disease and lower the effect of the therapies[15,16].

7. Neurobiological Mechanisms Underlying Cognitive and Functional Decline

Cognitive and functional decline in Parkinson's Disease (PD) is a result of intricate neurobiological processes, which involve several neurotransmitter systems, neural networks and protein aggregates that have become pathologically altered. The main and most typical characteristic of PD is the destruction of the dopaminergic neurons in the substantia nigra pars compacta, which results in the shortage of dopamine in the striatum and the disturbance of the basal ganglia-thalamocortical circuits. Although the progressive degeneration of the dopaminergic system accounts for the classical motor symptoms, even more, wide-spread neuropathological changes that impact cortical and subcortical areas plus the process of aging, explain the cognitive and functional decline[17,18].

The aggregation of alpha-synuclein protein into Lewy bodies is considered to be the main culprit behind the neuronal dysfunction in Parkinson's Disease (PD). Besides the damage done to dopaminergic neurons, the drugs also affect cholinergic, noradrenergic and serotonergic systems, which are the major players in the process of thinking, attention and executive function[18,19]. The distribution of Lewy bodies in the cortex, especially in the frontal, temporal and parietal lobes, can be used as a marker for the type of motor and cognitive deficits such as executive dysfunction, visuospatial deficits and memory that have been observed in PD patients[19,20].

The gradual decrease in the ability to perform daily activities is strongly associated with the cognitive deficits, as the disturbances in the areas of planning, multitasking and adaptive behavior caused by the disruption of the fronto-striatal and fronto-parietal networks. The taking of structural imaging studies has provided evidence of the presence of cortical thinning, reduced gray matter volume and white matter microstructural abnormalities in the regions which are associated with executive and motor control, thereby further explaining the progressive loss of independence[21,22].

8. Role of Neuroimaging and Biomarkers

Neuroimaging together with biomarkers has turned into a mainstay in the apprehension of Parkinson's Disease (PD) and in long-term cognitive and functional outcomes predictions. Among the structural and functional imaging methods, Magnetic Resonance Imaging (MRI), Diffusion Tensor Imaging (DTI) and functional MRI (fMRI) are for instance, the major ones which allow the evaluation of changes in both cortex and subcortex that occur through the progression of the disease. In the course of studies, it has been found that among the alterations in the brain regions' size and connection that are responsible for executive dysfunction, memory deficits and reduced independence in daily activities, there are cortical thinning, decreased gray matter volume and changed connection in fronto-striatal and parietal brain networks[23].

Decreased levels of Cerebrospinal Fluid (CSF) alpha-synuclein, tau and amyloid-beta are some of the biomarkers that molecularly characterize disease pathophysiology and the risk of dementia in Parkinson's disease. The combination of imaging and biomarker profiles significantly boosts prognostic accuracy; thus, it is possible to pinpoint individuals susceptible to fast cognitive or functional decline with the help of Decline[23,24].

One of the main advantages of using advanced neuroimaging is that they enable the monitoring of the therapeutic interventions, thereby helping to evaluate the efficacy of either pharmacological or non-pharmacological strategies in decelerating disease progression. In short, the intertwining of neuroimaging and biomarker data signals patient-centered management, early intervention and improved long-term outcomes for people with PD[24].

9. Impact of Therapeutic Interventions on Long-Term Outcomes

Therapeutic interventions in Parkinson's disease (PD) not only focus on the alleviation of motor symptoms but also on the preservation of cognitive function and the maintenance of independence in daily living activities. Pharmacological treatments are the mainstay of the management of motor symptoms, especially the dopaminergic treatments like levodopa and dopamine agonists. These medicines improve the three main problems of PD, namely bradykinesia, rigidity and tremor, but it is not clear how much they affect cognitive function and the extent to which this is consistent across patients among the very few studies that have attempted to assess cognitive outcomes because[25,26] given the high variability of effects, some patients may experience stabilization of executive function while others get no or even counterproductive effects.

Advanced therapies such as Deep Brain Stimulation (DBS) of the Subthalamic Nucleus (STN) or Globus Pallidus internus (GPi) not only provide long-term motor benefits but can also lessen the burden of medication. On the other hand, the cognitive outcome after DBS is often uncertain, as mild declines in verbal fluency or executive function have been reported in some studies, which highlights the importance of careful patient selection and cognitive assessment prior to surgery[27]. Continuous compounding therapies, such as levodopa-carbidopa intestinal gel or apomorphine, may also lead to improvements in quality of life and daily activities of the patients with motor fluctuations; however, the cognitive effects remain modest and should be further studied[28]. The importance of non-pharmacological interventions for long-term outcomes is now a consensus. Among these structured exercise programs, physiotherapy and occupational therapy are main players in the field of rehabilitation who work to develop motor performance, balance and the degree of independence in performing everyday activities. Cognitive rehabilitation and training, even though they are computerized or task-specific interventions, have successfully made the brain more efficient at specific tasks, e.g., executive function, attention and memory and these gains are reflected in the patients' performance in daily activities[25,28].

10. Quality of Life and Caregiver Burden

The Parkinson's Disease (PD) has a major impact on the patients' quality of life (QoL) and at the same time it is a great source of stress for the caregivers. In addition to the motor symptoms, the cognitive decline, depression, anxiety, disturbed sleep and autonomic dysfunction are the main contributors to the patient's diminished well-being and functioning, which

in turn affect the patients' social interaction, independence and daily living activities[29,30]. Research shows that non-motor symptoms are, especially the cognitive impairment and executive dysfunction, stronger predictors of the decreased QoL than the motor severity alone[29,31]. Caregivers taking care of patients with PD have to deal with a lot of physical, emotional and financial burdens. The severity of the disease, the mental capacity of the patient and the assistance required in daily living activities are some of the factors that affect the caregiver's burden. Stress levels that are too high in caregivers have been linked to the development of depressive symptoms, difficulty sleeping and overall health that is poorer, thus, it is the case that patient outcomes and caregiver well-being are related in both directions[32,33]. It is important to recognize caregiver strain early and to provide psychosocial support, education and respite care so that both the caregiver and the patient will stay healthy.

Quality of Life (QoL) interventions should be multifaceted and include addressing motor control, cognitive function and the psychosocial needs. Structured exercise, cognitive rehabilitation and occupational therapy can not only boost patients' functional capacities but also, let the stress be reduced and the coping strategies be strengthened through caregiver education and support group attendance[29,30,34]. Comprehensive care models that encompass patient and caregiver interventions simultaneously are able to raise overall QoL, lessen hospital admissions and slow down functional decline, thus, it is clear that holistic management is incredibly crucial in PD.

11. Emerging Insights and Future Directions

Recent breakthroughs in research related to Parkinson's Disease (PD) have led to a greater understanding of the mechanisms responsible for cognitive and functional decline which, in turn, have made it possible to develop new diagnostic and therapeutic approaches. One of the most important aspects of the emerging evidence is that it is facilitating the adoption of personalized medicine that includes genetic, molecular and neuroimaging biomarkers to classify patients based on dementia and disease progression risk factors[35,36]. These methods enable early detection of individuals who are at a high risk. This, in turn, allows for timely intervention and may even slow down the process of functional decline.

Researchers are looking into new types of treatment that are not related to the old dopaminergic ones. Non-invasive brain stimulation methods like rTMS and tDCS are giving hope to patients with PD to their better cognitive functioning and execution of difficult mental tasks, especially if they are simultaneously participating in a cognitive training program[36,37]. Therein, the neurorehabilitation techniques like administering and doing computer-based cognitive exercises are aiming to keep or improve daily living activities while slowing down the cognitive deficits' progression.

The merge of digital health technologies like the use of wearables and telemedicine is a game changer for the future of long-term monitoring and personalized care in PD. Being able to track motor and non-motor symptoms continuously enables the quick therapy alterations which directly improve the functional outcomes and the quality of life[37,38]. In addition to this, the research that is taking place concerning disease-modifying methods brings about the treatments that target alpha-synuclein (the culprit of PD) through immunotherapy and neuroprotective agents, which could be the reason for changing the course of the disease and hence the decrease of the cognitive and functional impairments that are commonly associated with PD over long periods.

All these new perspectives bring to light an important change in the way patients with PD are treated; the gradual shift towards being treated on the basis of personal needs according to the multi-domain management strategies. The verification of these interventions, the determination of their long-term efficacy and the integration into the standard clinical practice to maximize patient outcomes will be the crucial factors in the future research[35-38].

12. Clinical Implications

The long-term cognitive and functional outcomes in Parkinson's Disease (PD) are clinically relevant areas of knowledge, which can directly affect the practice, the management of patients and the planning of their care. By allowing the recognition of cognitive impairment, executive dysfunction and early functional decline to be the basis of the therapeutic progress, clinicians can carry out aimed interventions that not only protect independence but also increase the quality of life[39,40]. The management of patients with Parkinson's should resort to routine evaluations of all symptoms, which should include the use of specialized neuropsychological tests for comprehensive non-motor evaluations, in order to provide timely changes to the treatment plan and keep the care individual-based.

To optimize pharmacological treatments, the simultaneous pursuit of both motor symptom control and cognitive and neuropsychiatric consideration has to be the ultimate goal. The use of the newest methods, like Deep Brain Stimulation (DBS) or continuous infusion treatments, presupposes an ultimate evaluation of cognitive functioning of the patient before surgery in order to avoid adverse neuropsychological outcomes[41]. Non-pharmacological methods, such as cognitive rehabilitation, structured exercise and occupational therapy, have a very important place in the maintenance of functional abilities and in the attenuating of disability progression[42].

The support and education of caregivers are just as essential, since the burden imposed on them may have an unfavorable impact on patient outcomes and the compliance with the treatment protocols. The application of strategies that are focused on the caregivers, like support groups and respite care, together with the routine management will be beneficial not only for the patient but also for the caregiver[43].

To sum up, it is the employment of a holistic, multi-faceted approach targeting the motor, cognitive, functional and psychosocial aspects that will bring about the best results in the long-term management of Parkinson's Disease (PD).

13. Conclusion

One can consider Parkinson's disease (PD) to be a disorder that consists of various domains, one major being motor, while others are the cognitive and daily living domains mainly affected. The long-term outcomes of patients' lives, in general, are determined mainly by the interaction between the clinical features, genetics and neurobiology, with cognitive impairment and functional decline being the most important factors influencing quality of life and independence[44,45]. Longitudinal studies provide evidence for the heterogeneity in disease progression, thus the

individualized assessment and early identification of patients at risk for rapid decline become the major aspects[46].

Therapeutic interventions, whether pharmacological or non-pharmacological, are the most important measures to save and even improve the cognitive and daily functioning of the patient. High-tech therapies like DBS (deep brain stimulation) and continuous infusion can provide better motor outcomes, while exercise, occupational therapy and cognitive training will ensure functional independence and at the same time reduce the burden of non-motor symptoms[47]. Moreover, caregiver support has always been and will continue to be a major factor in determining the best patient outcome, as the health status of the caregiver is directly related to that of the patient[48].

Finding new biomarkers, neuroimaging and precision medicine are the methods of research in the future that will be able to do the long-term patient trajectories prediction and to smartphone-matching that treatment to the individual need. Emerging research in biomarkers, neuroimaging and precision medicine holds promise for predicting long-term trajectories and tailoring interventions to individual needs. Integrating these insights into clinical practice can enhance patient-centered care, delay functional decline and improve both cognitive and overall quality-of-life outcomes for individuals living with PD.

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