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A Scientific Approach Using Diagnostic Tools for the Pathogenesis Tailored Treatment of Parkinson's Disease

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ABSTRACT

Parkinson's disease (PD) is a common neurodegenerative disorder characterized by motor dysfunction and various non-motor symptoms due to the loss of dopaminergic neurons. Traditional treatments like L-DOPA and deep brain stimulation manage symptoms but don't address the root cause, leading to disease recurrence. Key factors in PD include genetic mutations in α-synuclein (α-syn) and leucine-rich repeat kinase 2 (LRRK2). α-syn aggregates and environmental toxins drive PD progression, with immunotherapy targeting α-syn showing promise. LRRK2 mutations increase kinase activity, linked to neuroinflammation, making LRRK2 inhibitors a potential treatment. Advancements in diagnostic technologies and biomarker research enhance PD diagnosis and enable tailored treatments. Combining these targeted approaches with traditional therapies aims to improve patient outcomes and quality of life by addressing the underlying causes of PD.

Abbreviations: CSF: Cerebrospinal Fluid; MPTP: 1-Methyl-4-Phenyl-1,2,3,6-Tetrahydropyridine; LRRK2: Leucine-Rich Repeat Kinase 2; PD: Parkinson's Disease ; α-syn: α-synuclein

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Parkinson's disease is the second most common neurodegenerative disease worldwide after Alzheimer's disease. The main symptom of Parkinson's disease is an impaired motor function, including tremors, rigidity, and bradykinesia. Other symptoms may include postural instability, anosmia, urinary incontinence, constipation, dysphagia, insomnia, depression, anxiety, and dementia [1]. As the world ages, the prevalence of Parkinson's disease continues to increase, and has recently become higher than the prevalence of cancer in the elderly population [2]. Therefore, there is increasing interest in the diagnosis and treatment of Parkinson's disease, and over the past decade, research on therapeutic targets, treatment drugs, and biomarkers has been actively conducted from academy to the industry.

The crucial pathology of PD is the loss of dopaminergic neurons in the substantia nigra pars compacta, and treatment has traditionally relied on providing additional dopamine through L-DOPA prescriptions [3]. Deep brain stimulation, which involves artificial electrical stimulation using a pacemaker, has also been employed as a treatment [4]. Recently, transplantation of tailored-dopaminergic neurons derived from stem cells has been applied to PD therapy [5]. However, these treatments do not eliminate the pathogens remaining in brain tissue, and because PD is likely to relapse without complete brain replacement, efforts are being made to develop treatments and diagnostic tools targeting these pathogens. The neurodegeneration of dopaminergic neurons is driven by genetic factors or environmental toxins, along with aging. Among genetic causes, α-synuclein (α-syn) is

a notable factor in the pathogenesis of PD and is a major component of Lewy bodies and Lewy neurites [6]. The aggregation of α-syn is related to the progression of PD and is affected by environmental toxins such as rotenone, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), 6-hydroxydopamine and paraquat. These toxins enhance oxidative stress in neurons, leading to the modification, interaction, and oligomerization of α-syn [7]. Therefore, many treatments have been studied to inhibit α-syn aggregation or boost the clearance of oligomeric α-syn. Immunization treatment using antibodies against α-syn oligomers is becoming more feasible as a treatment through clinical research [8].

Leucine-rich repeat kinase 2 (LRRK2) is another critical factor in PD and is considered a potential therapeutic target. Studies of genetic mutations in LRRK2 have demonstrated that upregulation of kinase activity is important for the pathogenesis of PD [9]. Increased LRRK2 kinase activity is also associated with oxidative stress and neuroinflammation [10,11], and idiopathic PD patients have shown increased LRRK2 kinase activity [12]. Therefore, drugs that specifically inhibit LRRK2 kinase activity are being studied as new PD therapies, with many researchers and industries around the world engaging in clinical research on LRRK2 inhibitors. The diagnosis of PD is still largely based on the judgment of medical experts using traditional methods. Recently, advancements in technology for live imaging of brain tissue and the application of artificial intelligence to improve image quality and resolution have supported more accurate diagnoses [13,14]. In addition to these technological advancements, research on diagnostic tools using PD biomarkers has also been conducted. Oligomeric α-syn and LRRK2 have been studied as representative biomarkers of PD. Biological fluids such as cerebrospinal fluid (CSF), serum, saliva, and urine have been used in diagnostic assay studies for α-syn oligomers and LRRK2 [15,16]. While it is important to uncover causal relationships with pathological causes through biomarker research using biological fluids, if PD pathogenesis can be diagnosed using these biomarkers, therapies can be tailored accordingly.

Diagnosing pathogens in PD patients using diagnostic tools is important to provide targeted therapeutic strategies to alleviate α-syn and LRRK2-driven pathology. α-syn aggregates and hyperactivated-LRRK2 will remain in brain tissue and continue to play a role in PD pathogenesis even after L-DOPA drug treatment or dopaminergic neuron transplantation. Evidence supporting this includes:

1. Studies suggesting that α-syn aggregates can transfer from existing host dopamine neurons to transplanted dopamine neurons, promoting disease progression [17-19].

2. The demonstrated transmission of α-syn via neuron-to-neuron or neuron-to-astroglia pathways [20-22] and

3. Reports elucidating that LRRK2 kinase activity is a key mediator of neuroinflammation in microglia and deficient neuroprotection in astrocytes [23-25].

For these reasons, unless the pathological causes are addressed, it is difficult to claim that PD has been completely cured simply by supplying dopamine through L-DOPA administration or transplanting dopamine neurons.It is presumed that tailored treatment according to the diagnosis of α-syn or LRRK2 pathogenesis can further increase therapeutic efficacy in the long term when combined with treatments that reinforce or regenerate the function of dopaminergic neurons. Therefore, pathological diagnosis will provide a sufficient basis for offering customized treatment to PD patients in the future, and such pathogenesis-tailored treatment will be able to provide patients with a satisfactory quality of life through synergistic effects when combined with other treatments.

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Conflicts of Interest

The authors declare no competing financial interests.

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