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Decoding Parkinson's Disease: Roles of Genes and Neuroinflammation – A Narrative Review

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Abstract. Parkinson's disease (PD) is a progressive neurodegenerative condition characterized by dopaminergic neuronal loss in the substantia nigra, which is accompanied by both genetic and inflammatory causes. Recent studies have highlighted the simultaneous importance of genetic predisposition and neuroinflammatory mechanisms in disease development, progression, and clinical heterogeneity. The present paper intends to review current research on the roles of neuroinflammation and genetic variables in PD etiology, as well as to assess their interplay, diagnostic relevance, and treatment promise. This narrative review brings together data from recent studies on monogenic mutations (e.g., SNCA, LRRK2, GBA1), inflammatory signaling pathways, glial cell dysfunction, experimental models, and biomarker research. Therapeutic developments addressing these processes are also discussed, with a focus on translational progress and new trends. The combination of neuroinflammation and genetics provides significant insights into the disease pathogenesis. A focus is observed on developing biomarkers and precision medicine approaches that target both pathways; this provides hope for an earlier diagnosis and more successful, tailored treatment strategies in the future.

Keywords: Parkinson's disease, neuroinflammation, genetic susceptibility, cytokines, pathogenesis, gene–environment interaction.

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Parkinsono ligos atkodavimas – genų ir neuroužd egimo vaidmuo: pasakojamoji apžvalga

Santrauka. Parkinsono liga yra progresuojanti neurodegeneracinė būklė. Esant šiai būklei įprastai pasireiškia dopaminerginis neuronų nykimas juodojoje medžiagoje, kurį dažniausiai sukelia tiek genetinės, tiek uždegiminės priežastys. Naujausi tyrimai pabrėžia, kad ligos raidai, tolesnei eigai bei klinikiniam heterogeniškumui vienodai svarbūs yra neuroužd egiminiai mechanizmai ir genetinis faktorius. Šiame straipsnyje siekiama apibendrinti naujausius tyrimus, nagrinėjančius neuroužd egimo ir genetinių kintamųjų vaidmenį Parkinsono ligos etiologijai, kartu įvertinant jų sąveiką, diagnostinę svarbą bei lūkesčius dėl gydymo proceso. Šioje pasakojamojoje apžvalgoje surinkti naujausių monogeninių mutacijų tyrimų (pvz., SNCA, LRRK2, GBA1), uždegiminio signalo kelių, glijinių ląstelių disfunkcijos ir biožymenų tyrimų duomenys. Taip pat apžvelgiamos terapeutinės inovacijos, kuriomis siekiama spręsti šių faktorių keliamas problemas, akcentuojant pažangą transliacijos srityje ir naujausias tendencijas. Neuroužd egimo ir genetikos faktorių sąveika teikia svarbių įžvalgų apie ligos patogenezę. Pažymėtina, kad formuojasi dviejų krypčių nuostata, kai iškart einama abiem keliais – kuriami tiek biožymenys, tiek tikslaus poveikio vaistai. Tokios tendencijos suteikia vilčių, kad taps įmanoma ankstyvesnė diagnozė ir ateityje bus parengtos labiau nusisekusios ir asmeniškiau taikomos gydymo strategijos.
Pagrindiniai žodžiai: Parkinsono liga, neuroužd egimas, genetinis polinkis, citokinai, patogenezė, genų ir aplinkos sąveika.

1. Introduction

Parkinson's disease (PD) is a progressive neurodegenerative disorder widely recognized for its motor symptoms (resting tremor, rigidity, bradykinesia, and postural instability) [1,2]. Patients may experience non-motor symptoms such as anosmia, constipation, depression, REM sleep behavior disorder, and cognitive abnormalities before experiencing characteristic motor signs [3]. PD is characterized by the loss of dopaminergic neurons in the substantia nigra pars compacta and other brainstem nuclei, as well as intraneuronal Lewy bodies formed of aggregated α-synuclein [3]. These alterations impair basal ganglia circuits, thus causing motor abnormalities. Pathology also affects noradrenergic, serotonergic, and cortical regions, resulting in a non-motor syndrome. The majority of PD cases are idiopathic; however, genetics play a significant role in a subset: approximately 5–10% of PD patients carry a highly penetrant mutation or monogenic syndrome [4,5]. Known PD genes include SNCA (α-synuclein), LRRK2, PRKN (parkin), PINK1, DJ-1, and others [4,5]. Notably, heterozygous mutations in GBA1 (glucocerebrosidase) are now recognized as the single biggest genetic risk factor for PD, sometimes resulting in an earlier onset and a more severe clinical course. Inflammation in PD appears to be a reaction to α-synuclein pathology and a cause of neuron loss [4,5]. The link between protein aggregation and immunological activation shows that PD is caused by a combination of genetic susceptibility, environmental factors, and abnormal immune responses [6].

A rising body of evidence suggests that neuroinflammation plays an important role in PD etiology [1,7]. Postmortem PD brains and animal models show persistent activation of brain immune cells (microglia and astrocytes) as well as higher amounts of pro-inflammatory mediators [7]. These glial cells produce cytokines and chemokines (e.g., TNFα, IL-1β, IL-6, IL-12) that might worsen neuronal damage [7]. In contrast, misfolded α-synuclein and other PD-related stresses trigger innate immune signaling in glia (e.g., via TLR/NF-κB and the NLRP3 inflammasome), producing a vicious cycle [1,2]. Thus, PD is now recognized as a complex disease in which age, genetics, and environmental factors converge on common pathways (including neuroinflammation) to cause neurodegeneration [1,7].

This narrative review aims to explore the intricate relationship between genetics and neuroinflammation in the pathogenesis of PD. By examining key genetic mutations, inflammatory mechanisms, and their interplay, the review seeks to highlight how these factors contribute to disease onset, progression, and heterogeneity. Additionally, it evaluates current and emerging therapeutic strategies targeting these pathways and discusses the role of biomarkers in advancing an early diagnosis and offering personalized treatment approaches.

2. Epidemiology and Clinical Features

PD is becoming more common, especially among the elderly [1,8]. According to global estimates, roughly 11.8 million people suffer from PD, with an age-standardized prevalence of about 139 per 100,000 and an annual incidence rate of about 15.6 per 100,000 people [8]. These numbers have gradually scaled up in recent decades and are projected to more than double by 2050, due primarily to an increased life expectancy, resulting in population aging [9]. PD is mainly a disease of the elderly, with its incidence increasing dramatically after the age of 60 and peaking between the ages of 80 and 84 [8,10]. Age is the most prominent risk factor for the disease, while it is estimated that roughly 4% of cases manifest before the age of 50, a condition known as young-onset PD [8,10]. A male-to-female ratio of 1.4 to 2:1 indicates that men are more likely to be diagnosed with PD [8,10]. This difference in gender has been attributed in part to estrogen's neuroprotective impact, as seen by studies revealing an increased PD risk among women with a shorter estrogen exposure, such as those who suffer an early menopause [8,10]. Geographic disparities in PD prevalence have also been identified. The largest rates are found in North America and Europe, with a lesser incidence in Asia [10]. These variances may reflect not only population age associations, but also differences in diagnostic methods, environmental exposures, and lifestyle factors [8,9].

Both the motor and non-motor aspects of the clinical presentation of PD are highly variable. Cardinal motor symptoms associated with the condition include bradykinesia, resting tremor, rigidity, and postural instability [1]. However, motor subtypes differ greatly among patients. Some people have a tremor-dominant phenotype with pronounced resting tremor and a relatively preserved gait and posture, whereas others have an akinetic-rigid or postural instability gait disorder (PIGD) phenotype with more severe bradykinesia, balance issues, and postural reflex impairment [1]. Tremor-dominant forms typically advance more slowly and respond better to levodopa therapy, whereas PIGD variations exhibit a rapid functional decline and an early start of comorbidities [1]. Data-driven subtyping projects have recently found unique progression trajectories in PD [11]. A longitudinal cohort study identified two major clinical subtypes: a slow-progressing group with minimal motor and cognitive involvement, and a fast-progressing group with prominent motor symptoms, early cognitive deterioration, and accelerated nigrostriatal dopaminergic degeneration [11]. Although early indications such as frequent falls, rapid gait decline, or cognitive impairment may indicate a more aggressive disease profile, patients with early-onset PD typically have a more benign course [12].

Aside from motor symptoms, PD is characterized by a wide range of non-motor manifestations that have a major impact on the quality of life and can occasionally precede motor signs [8,10]. These include neuropsychiatric symptoms (depression, anxiety, and apathy), cognitive impairment that leads to dementia, autonomic abnormalities (constipation, orthostatic hypotension, urine urgency), pain, exhaustion, and REM sleep behavior disorder [8,10]. Importantly, the severity and frequency of these symptoms differ substantially between individuals. For example,

dementia is more common in older people or those with glucocerebrosidase (GBA)-related genetic abnormalities [9,10].

A wide range of environmental factors influence PD risk and clinical variability. Chronic exposure to pesticides including paraquat and rotenone, as well as heavy metals, has been firmly related to an increased risk of PD via processes involving mitochondrial dysfunction and oxidative stress [8]. Rural lifestyle and agricultural activities are also related to a higher risk, most likely due to an increased exposure to these chemicals [8]. Epidemiological studies have repeatedly found that those who smoke tobacco or drink caffeine had a lower risk of PD, while the reasons behind these relationships are still unclear [8,10]. Nicotine may protect neurons via nicotinic acetylcholine receptors, but coffee may inhibit adenosine A2A receptors [1,8].

3. Genetic Landscape

PD genetic variables include rare monogenic mutations as well as wide polygenic risk alleles [2,4]. Seven high-penetrance genes, including SNCA (α-synuclein), LRRK2, PRKN (Parkin), PINK1, PARK7 (DJ-1), GBA1, and VPS35, are traditionally linked to monogenic types of PD [2,4,13]. Mutations in these genes are responsible for a significant number of familial PD cases. SNCA missense mutations or multiplications (duplications/triplications) cause autosomal-dominant PD by increasing α-synuclein toxicity, while PRKN, PINK1, and DJ-1 mutations are typically autosomal-recessive and associated with early-onset PD, frequently linked to mitochondrial dysfunction and impaired mitophagy [13,14]. DJ-1 mutations, in particular, contribute to juvenile-onset PD by impairing oxidative stress responses. The LRRK2 G2019S mutation is the most common cause of PD globally, accounting for up to 10% of familial and ~1–2% of sporadic cases with varied penetrance [13,14]. Importantly, GBA1 mutations, which are frequently heterozygous and without Gaucher disease, are seen in 5–15% of PD patients, particularly those of European descent [15]. These mutations dramatically raise the risk of acquiring PD and are linked to an earlier onset, a larger cognitive decline, and a faster motor progression [15,16]. In clinical terms, GBA1-associated PD is more severe than idiopathic PD, whereas LRRK2-associated PD closely matches the idiopathic type but progresses at a different rate [13–16].

Aside from monogenic mutations, common genetic variants add to polygenic risk. GWAS have found dozens to hundreds of PD risk loci [17]. Early GWAS identified connections near SNCA, MAPT, HLA-DRB, and BST1, thereby indicating α-synuclein regulation, tau biology, and innate immunity [17]. More recent and comprehensive GWAS meta-analyses, including multi-ethnic studies with tens of thousands of patients, have verified and increased this list [17]. A major 2022 multi-ancestry GWAS verified 66 known loci and identified 12 new ones, including genes related to autophagy, mitochondrial dynamics, lysosomal function, and immunological pathways [18].

Over 100 different genetic areas have been related to PD as of 2024 [16]. A big European GWAS, for example, detected 90 risk markers across 78 regions among 37,688 PD cases [17]. Polygenic risk scores (PRS), estimated to be ~1800 common variants, now explain 16–36% of heritable PD risk [17]. Those in the highest quintile of PRS had a 2–3-times higher lifetime risk than those in the lowest quintile. Polygenic risk accounts for approximately 70% of heritable vulnerability in sporadic PD [17].

Ongoing research in non-European groups (East Asian, South Asian, Latino, and African) has helped find population-specific risk alleles and fine-map previously known loci [17]. Furthermore, uncommon variations are emerging as multi-omics, transcriptome-wide, and single-cell

sequencing methods are becoming more widely used [16,17,19]. These discoveries are accelerating the development of precision medicine, as genetic heterogeneity explains not merely disease vulnerability but also phenotypic differences in disease progression, treatment response, and cognitive trajectory [16,17,19]. Polygenic profiling is thus emerging as a useful clinical technique for risk assessment, prognostic modeling, and treatment targeting.

4. Molecular Mechanisms of Neuroinflammation

Neuroinflammation is an important contributor to PD pathogenesis, mainly caused by prolonged activation of glial cells such as microglia and astrocytes, as well as the continuous production of inflammatory mediators [2,7,20]. Microglia (the brain's resident macrophages) are chronically activated in both PD patient brains and experimental models, particularly in the substantia nigra and adjacent neuronal circuits [2,7,20]. Microglia that are activated take on a phagocytic, amoeboid morphology and adopt a pro-inflammatory M1 phenotype, releasing high levels of cytokines like TNF-α, IL-1β, IL-6, IL-12, and IFN-γ, as well as chemokines like CCL2 (MCP-1), CCL3, CCL4, and CXCL1 [1,21]. These inflammatory mediators lead to a toxic brain microenvironment, directly harming dopaminergic neurons [1,21].

Aggregated α-synuclein activates microglia via interacting with Toll-like receptors (TLR2 and TLR4) and activating the NLRP3 inflammasome [1]. The inflammasome complex promotes the cleavage of pro-IL-1β into its active form, IL-1β, which increases neuroinflammation [20,21]. Mutant LRRK2 in microglia increases the production of TNF-α, IL-1β, and IL-6, while decreasing anti-inflammatory cytokine IL-10, thereby perpetuating the inflammatory cycle [20,21]. These cytokines engage intracellular signaling pathways including NF-κB, MAP kinases, and JAK-STAT (via IFN-γ) [20,21]. TNF-α and IL-1β stimulate NF-κB in neurons and glia, leading to transcription of additional inflammatory genes [20,21]. Furthermore, these cytokines increase the expression of iNOS and COX-2, which produce NO, superoxide, peroxynitrite, and prostaglandin E_2 [20]. These reactive oxygen/nitrogen species (ROS/RNS) are extremely cytotoxic, contributing to continuing neuronal death [20].

Beyond microglia, astrocytes play a crucial role. Reactive astrocytes emit complement proteins (such as C1q and C3), as well as cytokines and chemokines, while losing their neuroprotective characteristics [21]. These glial cells contribute to the recruitment of peripheral immune cells into the CNS by upregulating adhesion molecules and producing chemokines such as MCP-1/CCL2 and CXCL10, which promote monocyte and T cell infiltration [21].

Chronic neuroinflammation reinforces itself via increasing α-synuclein aggregation and stimulating TLRs on microglia, prolonging the cycle of inflammation and degeneration [1,20,21]. Aging exacerbates this process, as older microglia have higher amounts of TLR4, MHC-II, and other activation indicators, making them more vulnerable to inflammatory stimuli [1,20,21]. The neuroinflammatory landscape in PD is characterized by elevated pro-inflammatory cytokines (TNF-, IL-1, IL-6, IFN-), Increased chemokine signaling (CCL2, CXCL10), Hyperactivation of the NF-B, MAPK, JAK-STAT, and NLRP3 inflammasome pathways, and production of neurotoxic free radicals (NO, ROS, RNS) [1,20,21]. These processes establish a vicious cycle in which inflammation fuels neurodegeneration, which, in turn, amplifies inflammation, thus making neuroinflammation a critical target for future PD therapy [1,20,21].

5. Interplay Between Genetic Factors and Inflammatory Processes

Neuroinflammation in PD is not simply a result of neurodegeneration, but it is also influenced by genetic predisposition [1,2]. Multiple PD-risk genes influence the immunological response within the brain, namely, glial cell activity [1,2]. One of the most researched genes is LRRK2, which is strongly expressed in microglia and monocytes [14]. Mutations like G2019S and R1441G cause microglia to produce pro-inflammatory cytokines including TNF-α, IL-1β, and IL-6, and activate the NF-κB pathway [1,2]. LRRK2 inhibition has been demonstrated to diminish glial activation and cytokine production, thereby implying that it plays a role in making microglia more sensitive to inflammatory stimuli [14].

GBA1 mutations decrease lysosomal glucocerebrosidase (GCase) activity, causing lipid accumulation and increased microglial density [22]. When exposed to α-synuclein, GBA1-deficient microglia and astrocytes produce more pro-inflammatory cytokines [22]. GBA-PD patients have greater levels of peripheral cytokines, including IL-1β, IL-8, and TNF-α, compared to idiopathic PD [14,15]. PARK2 and PINK1, involved in mitochondrial quality control, often decrease inflammation by degrading inflammatory signaling adapters such TRAF2/6 and restricting NF-κB/JNK signaling [2]. Mutations in these genes increase inflammasome activation and IL-1β production, especially after exposure to stressors like LPS. This leads to an enhanced dopaminergic neuron loss in knockout models [2]. DJ-1 also influences glial immunity; its absence causes hyperactive microglial responses to many inflammatory stimuli [2]. SNCA (α-synuclein) mutations or overexpression affect microglial behavior [2]. Extracellular α-synuclein aggregates activate microglia through TLR2 and the NLRP3 inflammasome, leading to increased cytokine production [2,15]. Overexpression of α-syn in microglia causes neurotoxicity and dopaminergic cell death [2,15]. These findings are supported by GWAS, which show that numerous PD-associated variations are found in immune-related loci such as HLA and BST1, as well as regions active in microglia [18]. These genetic factors interact with environmental stimuli (such as viruses, toxins, and gut dysbiosis), indicating a gene-environment synergy [18]. For example, systemic inflammation or gut-derived signals may cause excessive microglial activation in genetically predisposed people [18].

PD risk genes appear to distort the balance of neuroinflammation, either by increasing pro-inflammatory glial responses or decreasing anti-inflammatory control [19]. This interplay contributes to disease heterogeneity and progression while also highlighting possible treatment targets at the junction of genetics, immunology, and neurodegeneration [19].

6. The Central Role of Glial Cells

Microglial activation is critical in PD's neuroinflammatory condition. Postmortem examinations typically show an increase of reactive microglia in the substantia nigra pars compacta (SNpc), particularly around degenerating dopaminergic neurons [23]. These microglia upregulate inflammatory and immunological markers such as HLA-DR, CD68, CR3 (CD11b/CD18), CD23, ferritin, ICAM-1 (CD54), LFA-1 (CD11a), MHC class II, and CD86 [23-25]. Other PD-affected regions, such as the putamen, hippocampus, and temporal cortex, contain higher concentrations of MHC class II-positive microglia than the SNpc [23–25]. Activated microglia are more than just passive indicators of neuronal distress; they also play an active role in PD development [23–25]. When activated, they produce significant quantities of pro-inflammatory cytokines like TNF-α, IL-1β, IL-6, and IFN-γ, as well as enzymes like iNOS and COX-1/2 [7,23–25]. Microglia create reactive oxygen species (ROS) through NADPH oxidase (especially the gp91^phox sub-

unit), causing extracellular free radicals to harm neurons [23]. Imaging studies in early-stage PD show an inverse relationship between microglial activation and dopamine transporter availability, mirroring motor decline [24,26]. Experimental models, including MPTP-treated animals and human MPTP exposure cases, show that dopaminergic impairment triggers a robust and prolonged microglial response, sustaining a self-perpetuating loop of neuroinflammation and oxidative stress [23,24,26,27].

The innate immune system, which consists of neutrophils, dendritic cells, macrophages, and microglia, protects against pathogens and injuries by generating harmful chemicals such as cytokines, quinolinic acid, arachidonic acid metabolites, excitatory amino acids, and ROS [1,7,26]. Microglia are the primary ROS generators in the central nervous system, with input from mitochondrial oxidative phosphorylation (especially complex I and ubiquinone) [1,7,23]. ROS include superoxide, hydroxyl radicals, singlet oxygen, hydrogen peroxide (H_2O_2), reactive nitrogen (e.g., NO, peroxynitrite), and chlorine species (e.g., HOCl) [1,7,23]. While the body uses antioxidants like superoxide dismutase (SOD), catalase, glutathione (GSH), and vitamins C and E to counteract ROS, excessive accumulation causes oxidative stress, resulting in inflammation and neuronal damage [1,7,23]. Dopamine metabolism generates ROS, including H_2O_2 and dopamine-quinones, through monoamine oxidase (MAO) activity and autooxidation, making dopaminergic areas, particularly the SN, more susceptible [27]. Furthermore, excess NO becomes neurotoxic, especially when combined with superoxide to form peroxynitrite, a membrane-permeable oxidant that causes severe intracellular injury by protein nitration and S-nitrosylation [23].

The early and significant reduction (by 40–50%) of GSH in the SN, a major antioxidant responsible for ROS detoxification, is a characteristic of PD [7,23]. This decrease in GSH levels precedes other clinical symptoms such as mitochondrial complex I dysfunction and may not be caused by defective synthesis, but rather by an increased consumption or interaction with oxidized dopamine [7,23]. Notably, SN neurons have lower baseline GSH and are more vulnerable to age-related oxidative stress, which may explain why PD risk increases with age [23]. Oxidative stress causes widespread molecular damage [1,23]. High quantities of nitrated proteins, particularly α-synuclein, in Lewy bodies indicate oxidative damage. S-nitrosylation of essential proteins, such as parkin, disrupts the ubiquitin-proteasome pathway, thereby preventing protein breakdown [1,7,23]. Other signs include elevated protein carbonyls, heme oxygenase-1, and advanced glycation end products, which are mostly seen in the SN and indicate oxidative pathology distinct from incidental Lewy body disease [23].

Astrocytes, another kind of important glial cell, also significantly changes in PD. In response to microglial-derived cytokines, many astrocytes, which are normally supportive, develop a reactive phenotype ('A1' astrocytes) [26]. Reactive astrocytes lose their neuroprotective and homeostatic activities, releasing neurotoxic chemicals such TNF-α, IL-1β, IL-6, IFN-γ, nitric oxide, glutamate, and ROS [7,26]. Astrocytes can collect and propagate α-synuclein across neural circuits. Dysfunctional astrocytes also fail to buffer extracellular glutamate or recycle neurotransmitters, which worsens excitotoxicity and neuronal damage [26].

Importantly, microglia and astrocytes engage in complicated cross-talk that exacerbates neurodegeneration [26]. Microglial activation can turn astrocytes into hazardous A1 phenotypes, whereas astrocytes can affect microglial behavior via complement proteins and chemokines [26]. Chronic microgliosis, astrocytic reactivity, and their continuous signaling loop comprise a self-perpetuating inflammatory network in PD [26]. Excessive cytokine production, poor α-synuclein phagocytosis, and persistent inflammation lead to dopaminergic neuron death and disease development [27].

7. Insights from Animal Models and *In Vitro* Studies

The function of neuroinflammation and dopaminergic neuron degeneration has been explored by using PD experimental models. Neurotoxic models such as MPTP in mice and 6-hydroxydopamine (6-OHDA) in rats cause selective degeneration of dopaminergic neurons in the substantia nigra, mimicking PD motor and behavioral symptoms [10,24,28]. These models often show strong microglial activation and secretion of proinflammatory cytokines including TNF-α and IL-1β in afflicted areas like the striatum and midbrain [10,24,28]. In these models, astrocytes are also stimulated, causing reactive astrogliosis and the release of proinflammatory mediators and free radicals that worsen neuronal damage [24,28].

Glial cells have an important role in PD development, according to in vitro and in vivo studies [2,24]. Microglia, the brain's resident immune cells, play a critical role in this neuroinflammatory process [2,24]. When activated by pathogenic stimuli, like α-synuclein aggregation or dopaminergic degeneration, microglia exhibit a proinflammatory (M1-like) behavior [2,24]. They produce cytokines such as TNF-α, IL-1β, IL-6, and IFN-γ, as well as upregulate inflammatory markers such MHC class II, CD68, and CD86 [2,24]. Furthermore, they generate reactive oxygen species (ROS) largely through the NADPH oxidase complex, namely its gp91^phox component, leading to oxidative stress and dopaminergic neuron death [2,24]. Chronic microglial activation has been found in postmortem PD brains, particularly in the SN and other afflicted areas such as the putamen and hippocampus and is associated with disease severity [2,24].

Studies on *Caenorhabditis elegans* (C. elegans) have brought light on the toxicity caused by α-syn. Garry Wong's team produced an early model in 2003 which involves overexpressing both wild-type and A53T mutant versions of α-syn using neuron-specific promoters [29]. GFP tagging revealed dopaminergic neurodegeneration in these transgenic worms [29]. In contrast to human PD, the deterioration did not progress with age. Nonetheless, these models are still valuable for studying modulators of dopaminergic function [29]. Overexpressing human α-synuclein (wild-type or mutant A53T) in mouse models leads to elevated endogenous dopamine (DA) levels, which correspond with neuronal loss and motor dysfunction [29]. This suggests that an interaction between DA and α-syn contributes to selective neuron vulnerability [29]. Injecting pre-formed α-syn fibrils (PFF) into mice leads to increasing Lewy-like pathology and activation of inflammasomes such as NLRP3, suggesting glial involvement in disease development [29]. Genetic models with LRRK2, PINK1, or GBA mutations show that these PD-related genes predispose animals to increased inflammatory responses to immunological stress, emphasizing gene-environment interactions [2,29]. For example, PINK1 deficiency in glial cells exacerbates inflammation-induced dopaminergic death, whereas LRRK2 or GBA mutations in human iPSC-derived microglia cause increased cytokine production when activated [2,29].

A crucial pathogenic characteristic of PD is oxidative stress. Microglia, macrophages, and astrocytes produce ROS and reactive nitrogen species (RNS) through NADPH oxidase, mitochondrial failure, and iNOS activity [23,30,31]. Dopamine metabolism produces hydrogen peroxide (H_2O_2) and dopamine-quinones, which destroy cellular components, thus making dopaminergic neurons especially sensitive [23,30,31]. Peroxynitrite, which is generated when nitric oxide and superoxide react, causes severe intracellular damage [23,30,31]. Excess ROS alters proteins, lipids, and nucleic acids, resulting in pathological indicators such as nitrated α-synuclein and S-nitrosylated parkin that disrupt the ubiquitin-proteasome system [23,30,31]. Additionally, the glutathione (GSH) antioxidant system is considerably depleted in PD patients' SN, by 40–50%. This impairment frequently precedes other clinical symptoms, such as mitochondrial complex I

failure, and it may be caused by an increased consumption or dopamine responses rather than defective synthesis [23,30,31]. Necroptosis, a kind of inflammatory cell death triggered by TNF-α signaling, has been linked to PD [23,24,30,31]. Studies have shown that suppressing necroptosis using necrostatin-1 protects dopaminergic neuron loss in toxin-induced mice. This emphasizes the importance of inflammation-induced cell death in PD development [23,24,30,31].

However, while animal and cellular models provide mechanistic insights, they are limited nevertheless [30]. For example, MPTP is highly poisonous in humans but less so in rodents, necessitating the use of adjuncts such as probenecid to increase toxicity [30]. Rodents process environmental toxins differently and may not fully mimic human α-synuclein disease or PD's chronic development [30,31]. Motor function tests may also fail to detect illness symptoms that are unique to a particular species [30,31]. Thus, while these models are still important for linking PD genes to inflammation and degeneration, discoveries must still be verified in human tissues to close the translational gap, especially since many promising anti-inflammatory medicines in rodents have failed in clinical trials [30,31].

8. Biomarkers and Neuroimaging in Assessing Neuroinflammation

An early detection and effective monitoring of PD rely heavily on the identification of reliable biomarkers and improved neuroimaging techniques (**Figure 1** outlines the use of structural and functional imaging to diagnose and manage various Parkinsonian syndromes). Biomarkers are critical for early-stage PD diagnosis, disease progression tracking, and therapy response evaluation. Molecular biomarkers such as α-synuclein, tau, and amyloid-β42 (Aβ42) in CSF, blood, and other body fluids have been widely studied for their relationship with neurodegenerative processes in PD [1,23–25,32]. Since acquisition of live neuronal tissue is a highly invasive procedure, CSF is an excellent surrogate for studying central nervous system disorders. Neuroinflammation plays an essential role in PD development, and inflammatory biomarkers are being studied to represent this component [23–25,32]. PD patients have elevated levels of cytokines like IL-1β, IL-2, IL-6, IL-10, TNFα, and soluble TNF receptors (sTNFRs) in their cerebrospinal fluid and blood [23–25,31]. Promising peripheral biomarkers include hsCRP, RANTES/CCL5, MCP-1, soluble TREM2, fractalkine (CX3CL1), and exosomal α-synuclein [1,23–25,32]. Alterations in these inflammatory mediators point to both central and peripheral involvement in PD pathogenesis, possibly via the gut-brain axis. Notably, subsets of individuals with GBA mutations may exhibit greater biomarker evidence [1,23–25,32].

Neuroimaging enhances fluid biomarkers by observing structural and inflammatory changes *in vivo* [33]. Standard MRI sequences are generally used to rule out secondary causes of parkinsonism, including basal ganglia tumors, granulomas, calcifications, vascular abnormalities, Wilson's disease, and hydrocephalus [33]. More advanced MRI techniques, such as inversion recovery sequences that attenuate gray and white matter signals, have demonstrated potential in detecting hypointensity in PD patients' lateral substantia nigra [33]. However, this method is complicated and currently lacks diagnostic sensitivity due to the overlap with normal imaging patterns [33].

Transcranial sonography (TCS) is another noninvasive imaging technique [34]. It detects midbrain hyperechogenicity, which is thought to be caused by an increased iron deposition and may serve as a phenotypic marker for PD risk [34]. Echogenicity has been reported even in presymptomatic people with mutations in genes such as α-synuclein, LRRK2, parkin, and DJ1 [34]. TCS has shown promising results, with a claimed sensitivity of up to 91% and a specificity of

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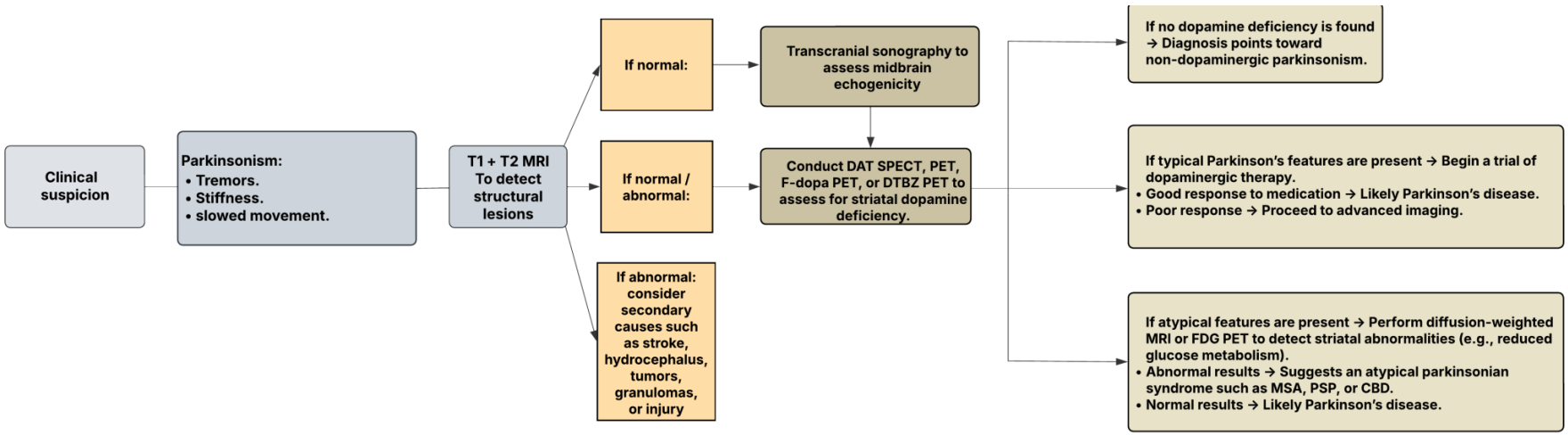

Figure 1. Parkinson's disease imaging algorithm. (This figure is adapted with modifications from Brooks et al. (2010), Imaging Approaches to Parkinson. Disease, Journal of Nuclear Medicine [33])

Note. DAT SPECT: Dopamine Transporter Single-Photon Emission Computed Tomography; PET: Positron Emission Tomography; F-dopa PET: Fluorodopa Positron Emission Tomography; DTBZ PET: Dihydrotetrabenazine Positron Emission Tomography; MRI: Magnetic Resonance Imaging; FDG PET: Fluorodeoxyglucose Positron Emission Tomography; MSA: Multiple System Atrophy; PSP: Progressive Supranuclear Palsy; CBD: Corticobasal Degeneration.

roughly 82% when compared to the final clinical diagnosis, for an overall accuracy of 88% [34]. Nonetheless, its diagnostic utility is restricted by a few factors: up to 10% of people lack an appropriate acoustic bone window, and motion aberrations from severe tremors can disrupt image capture [34]. Furthermore, enhanced echogenicity has been observed in non-PD populations, including patients with essential tremor, depression, and even some healthy controls, thereby lowering specificity [34].

PET imaging using ligands targeting the translocator protein (TSPO), a marker of active microglia, is utilized to detect neuroinflammatory alterations [32]. Ligands [^11C]PK11195, [^18F] FEPPA, and [^11C]PBR28 show increased binding in the midbrain and striatum of PD patients, thereby indicating microglial activation [32]. Other PET tracers being studied are [^11C] DAA1106 and [^11C]DPA-713 [32]. The interpretation of TSPO PET data is restricted by factors such as low signal intensity and individual variability caused by TSPO gene polymorphisms [32].

Additional imaging techniques, like susceptibility-weighted imaging (SWI), quantitative susceptibility mapping (QSM), and diffusion-weighted imaging, are being evaluated for their capacity to detect iron accumulation and microglia-related diffusion alterations [33,34]. Although these modalities have demonstrated promise in research settings, they require additional validation and standardization in terms of protocol, ligand selection, and quantitative analysis before clinical use [33,34].

9. Current Therapeutic Approaches

Several clinical and preclinical studies have investigated neuroinflammation as a potential disease-modifying therapy for PD. Several pharmaceutical methods have been investigated, including non-steroidal anti-inflammatory drugs (NSAIDs), glucocorticoids (GCs), and new compounds [35–40]. NSAIDs such as ibuprofen have been demonstrated in epidemiological studies to reduce Parkinson's risk by up to 46%; however, clinical trials have not consistently validated these benefits, most likely due to methodological and functional differences between medications [40]. Since their clinical introduction in the 1950s, glucocorticoids, one of the most potent anti-inflammatory agents, have been associated with elevated plasma cortisol levels in PD patients, which appear unrelated to disease duration or L-DOPA use but may be linked to circadian rhythm disruption and impulsive behaviors [37].

More targeted therapies are being developed. LRRK2 kinase inhibitors, such as DNL151 and DNL201/Biib122, are being studied in clinical trials to reduce microglial inflammation in patients with LRRK2 mutations [32,35]. MCC950 and Selnoflast, NLRP3 inflammasome inhibitors, demonstrated promise in preclinical PD models by lowering IL-1β release, reducing microglial activation, and preserving dopaminergic neurons [31,35]. Various treatments, such as anti-TNF biologics, CSF1R inhibitors, PPAR-γ agonists like pioglitazone, and Nrf2 activators like dimethyl fumarate, have shown neuroprotective or anti-inflammatory benefits in animal studies [38].

Immunotherapies targeting α-synuclein are also being investigated. PD01A vaccine and PRX002 monoclonal antibody are being evaluated for their potential for reducing extracellular α-synuclein and its associated inflammation [35]. In animal models, antisense oligonucleotides and RNA interference techniques effectively lower α-synuclein expression while maintaining dopaminergic neurons [36]. Ambroxol, a medication that improves glucocerebrosidase (GBA) function, may lower α-synuclein buildup and associated inflammation, especially in GBA mutation carriers [32].

Exenatide, a GLP-1 receptor agonist used for diabetes, proved its anti-inflammatory effects in early trials and is now being tested in a phase 3 clinical trial, despite previous big studies finding

no substantial slowing of disease progression [38]. Sargramostim (GM-CSF) has been shown to ameliorate symptoms of early idiopathic PD [35]. Rifaximin, a non-absorbable antibiotic, has been used to change the gut microbiota in PD patients with significant baseline inflammation, implying a gut-brain inflammatory link [35].

Therapeutic treatments include inhibiting microglial activation, neutralizing IL-1 and TNF, and preventing the A1 astrocytic phenotype [39]. Anti-TNF therapy in patients with inflammatory bowel disease was linked to a lower incidence of PD, providing support to the involvement of systemic inflammation in disease etiology [39]. Non-pharmacological treatments, including physical activity and dietary omega-3 fatty acids, have also showed promise in lowering neuroinflammatory markers in PD models [32].

Despite showing substantial promise in preclinical models, anti-inflammatory therapies for PD have yet to achieve robust clinical success [40]. However, a new wave of precision treatments that address both inflammation and genetic risk factors is emerging [40]. Ongoing trials are increasingly using biomarkers, such as PET imaging and CSF cytokine analysis, to better assess target engagement and identify responsive patient subgroups, opening the door for more tailored approaches to PD care [32].

10. Emerging Trends and Future Perspectives

Recent developments in PD research are pushing a trend toward precision medicine, which combines genetic, molecular, and inflammatory knowledge to produce disease-modifying treatments.

Neuroinflammation is widely recognized as a key pathogenic process [1,2]. Strategies aimed at microglial activation, cytokine signaling, and the gut-brain axis are being investigated, with the potential to personalize anti-inflammatory treatments [2]. Immunomodulatory elements, such GDNF or anti-α-synuclein vectors, can be used in gene and cell therapies [2,19].

The development of trustworthy biomarkers such as PET ligands, exosome assays, and blood-based indicators is critical for early detection, patient stratification, and therapy response tracking [19,41,42]. Future therapy techniques will most likely integrate genetic screening, targeted drug delivery, and inflammatory management to personalize interventions to specific patients [41,42]. Large-scale multi-omics investigations are being conducted to detect early-stage disease markers and guide individualized treatment [41,42]. Together, these developing techniques are denoted by the potential to shift PD care from symptomatic alleviation to genuine disease improvement [19,41,42].

11. Conclusion

PD is a complex neurodegenerative condition influenced by genetics, environmental exposures, and persistent neuroinflammation. Genetic advances have uncovered significant monogenic mutations, mainly in SNCA, LRRK2, and GBA1, that impact disease progression and inflammatory patterns in addition to conferring vulnerability. At the same time, emerging data suggests that glial-mediated neuroinflammation is at the root of the disease pathogenesis, with activated microglia and astrocytes contributing to dopaminergic neuron death via cytokine production, reactive oxygen species, and failed synaptic homeostasis. Precision medicine techniques are being used to target both α-synuclein aggregation and inflammatory pathways, while existing treatments just target symptoms. The creation of novel biomarkers, including fluid-based imaging, and genetic markers, offers considerable promise for early detection, disease activity monitoring,

and therapy efficacy evaluation. Despite the translational obstacles given by animal models and clinical variability, the confluence of genetic, immunological, and neurodegenerative findings is opening the door to customized, disease-modifying therapeutics. Continued interdisciplinary research will be required to translate these molecular insights into effective, customized therapies capable of changing the course of the disease.

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