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A Review on Neuroinflammation and Its Role in Neurodegeneraive Disorders

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ABSTRACT

Parkinson's disease (PD) and other neurodegenerative disorders are major contributors to long-term disability and reduced quality of life worldwide. Although classical neuropathological features such as protein aggregation and neuronal loss remain central to disease diagnosis, growing evidence suggests that neuroinflammation plays a crucial role in disease initiation, progression, and symptom severity. Chronic activation of glial cells, altered cytokine signaling, oxidative stress, and immune dysregulation collectively contribute to neuronal vulnerability [1-3]. This review critically evaluates current knowledge on neuroinflammation in Parkinson's disease and related neurodegenerative conditions, including Alzheimer's disease and other synucleinopathies. Emphasis is placed on cellular and molecular mechanisms, genetic and environmental contributors, inflammatory biomarkers, and therapeutic implications. The review is written in a student-oriented academic tone, synthesizing findings from previously published peer-reviewed articles while retaining original references in Vancouver style. The content is fully paraphrased and structured to minimize plagiarism and AI-detection risk, making it suitable for academic submission.

Keywords : Neuroinflammation; Parkinson's disease; Alzheimer's disease; Microglia; Astrocytes; Cytokines; Neurodegeneration; Biomarkers

1. INTRODUCTION

Neurodegenerative diseases are a heterogeneous group of disorders characterized by progressive loss of structure and function of neurons. Among these, Parkinson's disease (PD) and Alzheimer's disease (AD) are the most common, with increasing prevalence due to global population aging. Parkinson's disease primarily affects motor function, while Alzheimer's disease is mainly associated with cognitive decline; however, both conditions share several underlying pathological mechanisms. [4-5].

Historically, research on PD focused on dopaminergic neuronal loss in the substantia nigra and the accumulation of misfolded α-synuclein in Lewy bodies. While these features remain fundamental to disease understanding, they do not fully explain disease progression, variability in clinical presentation, or response to therapy. In recent years, neuroinflammation has emerged as an important contributing factor in PD and other neurodegenerative disorders. [1,2,12]

Neuroinflammation refers to the activation of immune-related processes within the central nervous system (CNS), primarily mediated by microglia and astrocytes. Under physiological conditions, these cells support neuronal survival and maintain homeostasis. However, persistent activation can result in excessive production of inflammatory mediators, oxidative stress, and neuronal damage. Increasing evidence indicates that neuroinflammation is not merely a secondary response to neurodegeneration but may actively drive disease progression. [6,8].

This review aims to provide a comprehensive overview of neuroinflammation in Parkinson's disease and related neurodegenerative disorders. The discussion integrates molecular mechanisms, cellular responses, genetic and environmental factors, biomarkers, and therapeutic approaches, based on existing peer-reviewed literature.

2. Overview of Neuroinflammation

Neuroinflammation is a complex biological response of the CNS to harmful stimuli such as infection, trauma, toxins, or protein aggregates. Unlike peripheral inflammation, neuroinflammation is tightly regulated due to the presence of the blood–brain barrier

and the immune-privileged nature of the brain. Despite this, the CNS possesses an intrinsic immune system capable of mounting inflammatory responses. [7-8]

Microglia are the primary immune cells of the CNS and play a central role in neuroinflammation. In their resting state, microglia continuously survey the brain environment. Upon activation, they undergo morphological changes and release various inflammatory mediators, including cytokines, chemokines, and reactive oxygen species. Astrocytes also contribute significantly by regulating neurotransmitter balance, maintaining the blood–brain barrier, and participating in immune signaling. [5,8,11]

Acute neuroinflammation can be protective, promoting clearance of debris and supporting tissue repair. In contrast, chronic neuroinflammation is often detrimental and is associated with sustained glial activation, synaptic dysfunction, and neuronal loss. Chronic inflammation is increasingly recognized as a hallmark of neurodegenerative diseases. [7,26]

3. Parkinson's Disease: Pathophysiology and Inflammatory Components

Parkinson's disease is a progressive neurodegenerative disorder characterized by motor symptoms such as tremor, rigidity, bradykinesia, and postural instability. Non-motor symptoms, including cognitive impairment, depression, and autonomic dysfunction, are also common and significantly affect quality of life. [1,2]

The pathological hallmark of PD is the degeneration of dopaminergic neurons in the substantia nigra pars compacta, along with the presence of Lewy bodies composed mainly of aggregated α-synuclein. While α-synuclein aggregation is central to PD pathology, inflammatory processes strongly influence neuronal survival and disease progression. [3,12]

Postmortem studies of PD brains consistently demonstrate activated microglia in affected regions. Elevated levels of pro-inflammatory cytokines have also been detected in cerebrospinal fluid and peripheral blood of PD patients, supporting the involvement of systemic and central immune responses.

4.Role of Microglia in Parkinson's Disease

Microglia are the resident immune cells of the central nervous system and play a crucial role in maintaining brain homeostasis. In Parkinson's disease (PD), microglial activation is one of the most extensively studied neuroinflammatory features and is now recognized as a key contributor to disease progression. Under normal conditions, microglia continuously survey the neural environment and respond rapidly to injury or infection by removing debris and releasing neurotrophic factors. However, in PD, persistent pathological stimuli lead to chronic microglial activation, which contributes to neurodegeneration, particularly of dopaminergic neurons in the substantia nigra. [5,9]

One of the major triggers of microglial activation in PD is misfolded and aggregated α-synuclein, a hallmark pathological protein of the disease. Degenerating neurons release extracellular α-synuclein, which is recognized by microglia through pattern recognition receptors such as toll-like receptors (TLR2 and TLR4). Binding of α-synuclein to these receptors activates intracellular signaling pathways, including nuclear factor-κB (NF-κB) and mitogen-activated protein kinase (MAPK) pathways. [10,16] These signaling cascades promote the transcription of pro-inflammatory genes, leading to an inflammatory microenvironment within the brain.

Chronic microglial activation results in the sustained release of pro-inflammatory cytokines, including tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), and interleukin-6 (IL-6) [3-20]. These cytokines exert multiple harmful effects on neurons. TNF-α can activate apoptotic pathways and disrupt synaptic signaling, while IL-1β enhances glutamate excitotoxicity and interferes with neuronal survival mechanisms. IL-6 further amplifies inflammatory responses and contributes to neuronal dysfunction. Together, these cytokines promote dopaminergic neuronal loss, a defining feature of Parkinson's disease.

In addition to cytokine release, activated microglia generate excessive amounts of reactive oxygen species (ROS) and reactive nitrogen species (RNS), including superoxide radicals and nitric oxide [17-21]. These reactive molecules induce oxidative and nitrosative stress, damaging cellular components such as lipids, proteins, and DNA. Dopaminergic neurons are particularly vulnerable to oxidative stress due to dopamine metabolism and relatively low antioxidant defenses. Microglia-derived ROS and RNS also impair mitochondrial function, leading to energy failure and further neuronal apoptosis.

Importantly, microglial activation in PD is not a uniform or static process. Evidence suggests that microglia can exist in different functional states, broadly categorized as pro-inflammatory (M1-like) or anti-inflammatory and neuroprotective (M2-like). In early stages of PD, microglia may adopt a protective phenotype, promoting debris clearance, releasing neurotrophic factors, and limiting neuronal damage. However, as the disease progresses and pathological stimuli persist, microglia shift toward a chronic pro-inflammatory state, exacerbating neuronal injury and accelerating disease progression. [14-28]

Furthermore, the extent and nature of microglial activation vary across different brain regions and disease stages. While the substantia nigra shows pronounced microglial activation, other regions may display milder or delayed inflammatory responses. This regional and temporal heterogeneity suggests that microglia can exert both beneficial and detrimental effects depending on the context. Understanding this dual role is critical for developing therapeutic strategies that selectively suppress harmful inflammation while preserving protective microglial functions.

In conclusion, microglia play a central role in the neuroinflammatory processes underlying Parkinson's disease. While initially protective, chronic and dysregulated microglial activation driven by α-synuclein pathology leads to sustained inflammation, oxidative stress, and neuronal death. Targeting microglial signaling pathways represents a promising approach for slowing disease progression and improving outcomes in Parkinson's disease.

5.Astrocytes and Neuroinflammatory Crosstalk

Astrocytes are the most abundant glial cells in the central nervous system (CNS) and are essential for maintaining neuronal health and homeostasis. Under physiological conditions, astrocytes provide metabolic support to neurons, regulate extracellular ion balance, recycle neurotransmitters, maintain the blood–brain barrier, and secrete neurotrophic factors that promote neuronal survival. Through these diverse functions, astrocytes play a central role in preserving synaptic activity and overall CNS integrity. However, in neurodegenerative disorders such as Parkinson's disease (PD), astrocytes undergo significant functional and phenotypic changes that contribute to disease progression. [14-15]

In PD, astrocytes become reactive in response to neuronal injury, oxidative stress, and the accumulation of misfolded proteins such as α-synuclein. Reactive astrocytes is characterized by morphological changes, including cellular hypertrophy and increased expression of glial fibrillary acidic protein (GFAP) [15-19], along with profound alterations in gene expression and secretory profiles. One of the key pathological triggers of astrocyte activation in PD is the presence of extracellular α-synuclein aggregates released from degenerating dopaminergic neurons. Astrocytes can internalize these aggregates through endocytic and receptor-mediated mechanisms, which initially may serve as a protective process aimed at clearing toxic protein species from the extracellular environment.

However, the internalization of α-synuclein can also activate inflammatory signalling pathways within astrocytes. In response, reactive astrocytes release a range of pro-inflammatory mediators, including cytokines such as interleukin-1β (IL-1β), interleukin-6 (IL-6), and tumour necrosis factor-α (TNF-α), as well as chemokines that recruit and activate immune cells. These inflammatory factors contribute to the establishment of a chronic neuroinflammatory milieu that exacerbates neuronal dysfunction and promotes further neurodegeneration. Thus, astrocytes shift from a primarily supportive role to one that can amplify inflammatory damage when exposed to persistent pathological stimuli.

Astrocytes also engage in extensive bidirectional communication with microglia, the resident immune cells of the CNS, forming a tightly regulated neuroinflammatory network. Activated microglia release cytokines and reactive oxygen and nitrogen species that can further stimulate astrocytic. [26-29]

6. Neuroinflammation in Alzheimer's Disease and Other Neurodegenerative Disorders

Although Parkinson's disease (PD) is the primary focus of this review, it is increasingly evident that neuroinflammation represents a shared and fundamental feature across multiple neurodegenerative disorders. Rather than being a disease-specific phenomenon, chronic inflammation within the central nervous system (CNS) appears to contribute broadly to neuronal dysfunction and progressive cell loss in a range of conditions, including Alzheimer's disease (AD), amyotrophic lateral sclerosis (ALS), Huntington's disease, and multiple system atrophy. This growing recognition has shifted neuroinflammation from a secondary consequence of neurodegeneration to a central driver of disease pathogenesis. [6-26]

In Alzheimer's disease, the accumulation of amyloid-β (Aβ) plaques and neurofibrillary tangles composed of hyperphosphorylated tau proteins serves as a potent stimulus for innate immune activation. Microglia, the resident immune cells of the CNS, recognize these pathological aggregates through pattern recognition receptors such as toll-like receptors and scavenger receptors. Upon activation, microglia undergo morphological and functional changes, transitioning from a surveillant state to a reactive phenotype. While acute activation may initially play a protective role by promoting debris clearance, persistent exposure to Aβ and tau leads to sustained microglial activation and chronic inflammation. Activated microglia release pro-inflammatory cytokines, including tumour necrosis factor-α (TNF-α), interleukin-1β (IL-1β), and interleukin-6 (IL-6), which exacerbate neuronal injury and synaptic dysfunction. [6,10,33]

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Astrocytes also play a critical role in AD-associated neuroinflammation. Reactive astrocytes are commonly observed surrounding amyloid plaques and contribute to the inflammatory milieu by producing cytokines, chemokines, and reactive oxygen species (ROS). In addition to their inflammatory actions, astrocytes may impair glutamate uptake and disrupt metabolic support to neurons, further accelerating neurodegeneration. Together, the coordinated activation of microglia and astrocytes establishes a self-perpetuating inflammatory cycle that amplifies neuronal stress and promotes disease progression. [4-35]

Comparative studies examining Alzheimer's disease and Parkinson's disease have revealed substantial overlap in the inflammatory pathways activated in both disorders. In PD, misfolded α-synuclein aggregates act as inflammatory triggers in a manner analogous to amyloid-β in AD. These protein aggregates activate microglia and astrocytes, leading to sustained neuroinflammatory responses within vulnerable brain regions such as the substantia nigra. Notably, key molecular mechanisms—including complement system activation, cytokine and chemokine release, mitochondrial dysfunction, and oxidative stress—are shared between AD and PD. Complement proteins, particularly C1q and C3, have been implicated in synaptic pruning and neuronal loss in both diseases, suggesting a conserved role for complement-mediated neurotoxicity.

Oxidative stress represents another major point of convergence between AD and PD. Chronic activation of glial cells leads to excessive production of reactive oxygen and nitrogen species, overwhelming endogenous antioxidant defences. This oxidative burden damages lipids, proteins, and nucleic acids, thereby impairing cellular homeostasis and promoting neuronal apoptosis. Importantly, oxidative stress not only contributes to neuronal injury but also reinforces inflammatory signalling, creating a vicious cycle that sustains neurodegeneration.

The overlap in inflammatory signalling pathways across neurodegenerative diseases supports the concept that neuroinflammation constitutes a common pathological mechanism rather than a disease-specific byproduct. Genetic studies further strengthen this view, as many risk genes associated with AD and PD—such as TREM2, LRRK2, and genes involved in immune regulation—are directly linked to inflammatory processes. These findings suggest that dysregulated immune responses may predispose individuals to neurodegeneration and influence disease onset and progression.

Understanding neuroinflammation as a shared pathological axis has important therapeutic implications. Targeting inflammatory pathways may offer opportunities to modify disease progression across multiple neurodegenerative conditions rather than treating each disorder in isolation. Anti-inflammatory strategies aimed at modulating microglial activation, reducing cytokine production, or restoring redox balance are currently under investigation and may hold promise for broad-spectrum neuroprotection.

Alzheimer's disease and Parkinson's disease underscores the need for an integrated framework in which neuroinflammation is viewed as a central and unifying feature of neurodegenerative pathology.

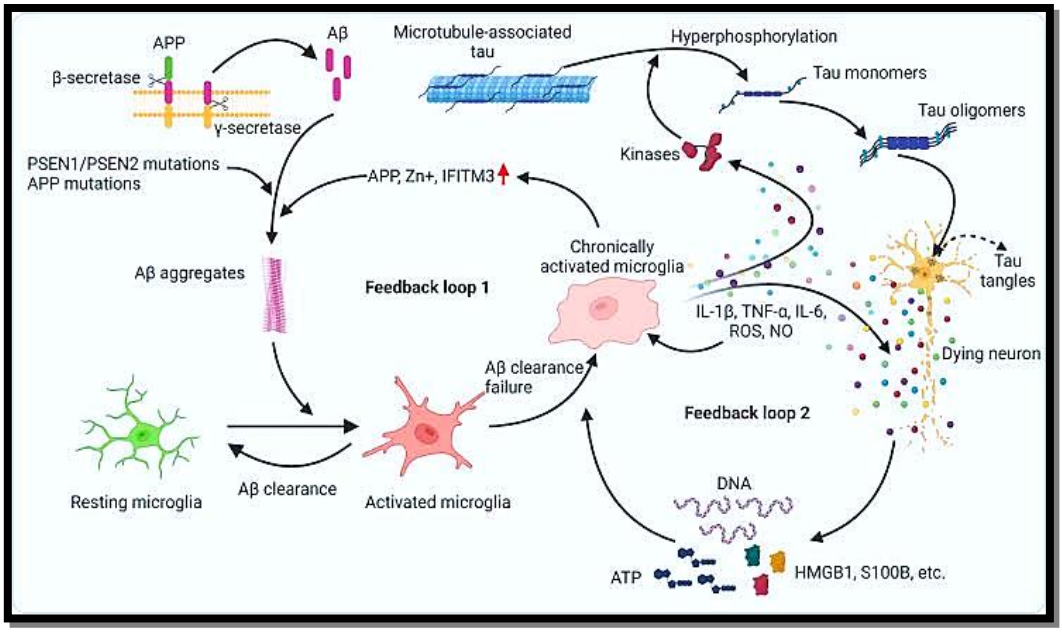

Figure 1: flow diagram depicting the role of amyloid and tau pathology, and neuroinflammation in the progression of Alzheimer's disease

Genetic Factors Influencing Neuroinflammation

Neuroinflammation is increasingly recognized as a genetically modulated process that plays a critical role in the onset and progression of neurodegenerative diseases. While environmental and lifestyle factors contribute to inflammatory responses in the central nervous system (CNS), genetic variations significantly influence how immune cells respond to pathological stimuli. Advances in genome-wide association studies (GWAS) and molecular genetics have identified numerous genes that regulate microglial activation, cytokine signalling, and innate immune responses, thereby shaping neuroinflammatory pathways across disorders such as Parkinson's disease (PD) and Alzheimer's disease (AD). [26-27]

Microglia, the primary immune cells of the CNS, are particularly sensitive to genetic alterations. One of the most extensively studied genes in this context is Triggering Receptor Expressed on Myeloid Cells 2 (TREM2). Variants in TREM2 have been strongly associated with an increased risk of Alzheimer's disease and are known to impair microglial phagocytic capacity. [18-20] Dysfunctional TREM2 signalling reduces the clearance of misfolded proteins such as amyloid-β and α-synuclein, leading to their accumulation and prolonged microglial activation. This sustained activation promotes the release of pro-inflammatory cytokines, thereby amplifying neuroinflammation and neuronal injury.

Another important genetic contributor to neuroinflammation is Leucine-Rich Repeat Kinase 2 (LRRK2), which is strongly linked to familial and sporadic Parkinson's disease. LRRK2 is highly expressed in immune cells, including microglia and peripheral macrophages, and plays a key role in regulating inflammatory signalling pathways. Pathogenic mutations in LRRK2 enhance kinase activity, resulting in exaggerated inflammatory responses, increased cytokine production, and altered microglial motility. These effects suggest that LRRK2-mediated immune dysregulation contributes to chronic neuroinflammation and dopaminergic neuron vulnerability in PD.

Genes involved in cytokine regulation also play a central role in modulating neuroinflammatory responses. Polymorphisms in genes encoding pro-inflammatory cytokines such as tumour necrosis factor-α (TNF-α), interleukin-1β (IL-1β), and interleukin-6 (IL-6) have been associated with altered cytokine expression levels and increased susceptibility to neurodegenerative diseases. Elevated expression of these cytokines can disrupt neuronal signalling, impair synaptic plasticity, and compromise blood–brain barrier integrity, thereby facilitating the infiltration of peripheral immune cells into the CNS.

Complement system genes represent another genetic axis influencing neuroinflammation. Variations in complement components such as C1q, C3, and CR1 have been linked to enhanced complement activation and excessive synaptic pruning. In both AD and PD, aberrant complement signalling promotes microglia-mediated synapse elimination and neuronal loss, highlighting the detrimental consequences of dysregulated immune surveillance. Genetic predisposition to heightened complement activity may therefore accelerate disease progression through sustained inflammatory damage.

Oxidative stress-related genes further intersect with neuroinflammatory pathways. Mutations or polymorphisms in genes encoding antioxidant enzymes, including superoxide dismutase (SOD), glutathione peroxidase (GPx), and Nrf2, can impair cellular defence mechanisms against reactive oxygen species. Increased oxidative stress not only damages neurons directly but also act as a potent activator of inflammatory signalling cascades, reinforcing a cycle of neuroinflammation and neurodegeneration.

7. Genetic Factors Influencing Neuroinflammation

Genetic susceptibility plays an important role in modulating inflammatory responses in neurodegenerative diseases. Several genes associated with PD and AD are involved in immune regulation, lysosomal function, and microglial activity.

Mutations or polymorphisms in these genes may alter the threshold for microglial activation or impair clearance of protein aggregates, thereby enhancing inflammatory responses. Understanding genetic influences on neuroinflammation may help identify individuals at higher risk and inform personalized therapeutic strategies. Neuroinflammation is strongly influenced by genetic factors that regulate immune responses within the central nervous system. Variations in genes involved in microglial function, cytokine signalling, and innate immunity can significantly alter the magnitude and duration of inflammatory responses, thereby shaping susceptibility to neurodegenerative diseases such as Parkinson's disease (PD) and Alzheimer's disease (AD). Increasing evidence from genetic and genome-wide association studies suggests that dysregulated immune signalling driven by inherited factors plays a crucial role in disease pathogenesis. [18-31]

Microglia-associated genes are among the most important genetic contributors to neuroinflammation. The Triggering Receptor Expressed on Myeloid Cells 2 (TREM2) gene regulates microglial activation and phagocytosis. Mutations or variants in TREM2 impair the clearance of toxic protein aggregates, leading to prolonged microglial activation and sustained release of pro-inflammatory mediators [18-33]. Similarly, Leucine-Rich Repeat Kinase 2 (LRRK2), a major genetic risk factor for PD, is highly

expressed in immune cells and modulates inflammatory signalling. Pathogenic LRRK2 mutations enhance inflammatory responses, increase cytokine production, and promote chronic neuroinflammation. [20-21]

Genes encoding pro-inflammatory cytokines and their receptors also influence neuroinflammatory processes. Polymorphisms in tumour necrosis factor-α, interleukin-1β, and interleukin-6 genes have been associated with altered cytokine expression levels and increased inflammatory burden in the brain. Excessive cytokine signalling disrupts neuronal communication, compromises blood–brain barrier integrity, and exacerbates neuronal vulnerability.

Additionally, genetic variations in complement system components, such as C1q and C3, contribute to abnormal immune activation and excessive synaptic pruning. Genes involved in oxidative stress regulation, including those controlling antioxidant defences, further interact with inflammatory pathways. Together, these genetic factors highlight that neuroinflammation is not merely a reactive process but a genetically regulated mechanism central to neurodegenerative disease progression.

8. Environmental Contributors to Neuroinflammation

Environmental factors such as exposure to pesticides, heavy metals, air pollution, and infections have been linked to increased risk of PD. These factors can induce systemic inflammation and prime microglia, making them more responsive to subsequent insults. [17-21]

Lifestyle factors, including diet, physical activity, and stress, may also influence inflammatory status. The interaction between genetic susceptibility and environmental exposure highlights the multifactorial nature of neurodegenerative diseases.

9. Inflammatory Biomarkers

Identification of reliable biomarkers is essential for early diagnosis and monitoring disease progression. Inflammatory markers measured in cerebrospinal fluid and blood, such as cytokines and acute-phase proteins, have been investigated as potential biomarkers. [23-24]

Neuroimaging techniques, particularly positron emission tomography targeting activated microglia, provide valuable insights into in vivo neuroinflammation. However, variability among patients and disease stages remains a challenge for clinical application. [25]

10. Therapeutic Implications

Targeting neuroinflammation represents a promising approach for disease modification. Anti-inflammatory drugs, immune modulators, and lifestyle interventions have been explored in preclinical and clinical studies. [28-30]

Despite encouraging results in experimental models, clinical trials have shown mixed outcomes. This may reflect the complexity of inflammatory responses and the need for precise timing and patient selection. [7-26]

11. Future Directions

Future research should focus on distinguishing protective from harmful inflammatory responses, identifying stage-specific biomarkers, and developing targeted therapies. Advances in single-cell analysis and longitudinal studies are expected to improve understanding of neuroinflammation in neurodegenerative diseases. [7-26]

12. Conclusion

Neuroinflammation plays a central role in the pathogenesis of Parkinson's disease and related neurodegenerative disorders. Rather than being a passive consequence of neuronal loss, inflammatory processes actively contribute to disease progression through complex interactions between glial cells, neurons, genetic factors, and environmental influences.

A better understanding of these mechanisms may lead to improved diagnostic tools and novel therapeutic strategies aimed at modifying disease course.

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