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Original Research Article

Neuroinflammation: A Common Link in Alzheimer's, Parkinson's, and Amyotrophic Lateral Sclerosis

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Abstract: Neurodegenerative disorders such as Alzheimer's disease (AD), Parkinson's disease (PD), and Amyotrophic lateral sclerosis (ALS) are significantly influenced by neuroinflammation. Cognitive and physical deficits result from the progressive death of neurones in central nervous system (CNS) caused through these disorders. The persistent activation of glial cells, including microglia and astrocytes, results in the continuous release of chemokines, pro-inflammatory cytokines, and other mediators that exacerbate neuronal death and damage; this is a characteristic of neuroinflammation. A buildup of misfolded proteins causes these inflammatory responses; examples of such proteins include huntingtin in HD, alpha-synuclein in PD, and amyloid-beta in AD. Chronic neuroinflammation accelerates neurodegeneration through oxidative stress, mitochondrial dysfunction, and disrupted neural transmission. Historical and recent research highlights the critical role of neuroinflammation, with early descriptions of PD, AD, and ALS dating back over 200 years. Emerging data from animal models indicate that persistent inflammatory responses contribute to neurodegenerative illnesses. Treatment strategies aiming to decrease neuroinflammation and, maybe, limit or stop disease progression require an understanding of the pathways of inflammation activation and their role in disease pathogenesis.

Keywords: Neuroinflammation, Amyotrophic lateral sclerosis, Parkinson's disease, Alzheimer's disease, Neurodegeneration

INTRODUCTION

Neurodegenerative ailment development is significantly influenced by neuroinflammation. The term neurodegenerative disorders refer to conditions where the central nervous system (CNS) gradually loses neurones, foremost to either physical infirmity or cognitive impairments, or both. Amyotrophic lateral sclerosis (ALS), Parkinson's disease (PD), and Alzheimer's disease (AD) are classic examples of classical neurodegenerative disorders [1], [2], [3].

The presence of glial cells, such as microglia and astrocytes, is indicative of neuroinflammation [4]. While these cells are necessary for maintaining CNS homeostasis and reacting to damage or infection, prolonged activation can be harmful. The release of pro-inflammatory cytokines, chemokines, and other mediators can worsen neuronal damage and death in a pathological state known as chronic neuroinflammation [5].

The buildup of misfold or protein aggression, like as amyloid-beta for Alzheimer's disease [6], alpha synuclein for PD [7], [8], and huntingtin for Huntington's disease [9], is hallmark for neurodegenerative illnesses. Glial cells recognise these protein clumps as toxic, resulting in a long-term inflammatory response. Additionally, hereditary variables and environmental triggers might contribute to the inflammatory environment [10].

Chronic neuroinflammation speeds up neurodegeneration by causing oxidative stress [11], mitochondrial dysfunction [12], and disruption of neural transmission. Knowing these processes are essential for creating treatment plans that try to reduce neuroinflammation and maybe slow or stop the course of neurodegenerative illnesses [13].

The neurodegenerative condition today known as PD was first defined therapeutically more than 200 years ago by James Parkinson. Conditions similar to Parkinson's disease (PD) have been recorded in traditional Indian writings about 1000 BC and

ancient Chinese medical records around 425 BC, despite the fact that this was the first official medical description [14]. Then came the descriptions AD in 1906 while amyotrophic lateral sclerosis (ALS) in 1869 [2].

Research on neurodegenerative illnesses first concentrated on neuronal destruction and general morphological alterations, including the accumulation of proteins like TAR DNA-binding protein - 43 (TDP -43), amyloid-beta (Aβ), and neurofibrillary tangles (NFTs) [15]. In 1975, it was first revealed that immune-related proteins were originate in the senile plaques of AD patients. Microglia activation was identified as a hallmark of neurodegenerative disorders in the 1980s [16], [17].

Even while inflammation may not often be the source of disease start, new evidence from a variety of animal models advocates that chronic inflammatory retorts comprising microglia and astrocytes are associated with the emergence of neurodegenerative disorders. Whether blocking these reactions may safely and efficiently halt or reduce the development of illness is a significant unresolved question. Addressing this requires an understanding of how inflammatory retorts are triggered throughout the CNS and how they contribute to illness [18].

This article summarises research on the inflammation-related traits mediated by the inborn and immunological systems in the development of Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis, and Multiple sclerosis (MS). It also identifies important topics for further study.

Immune system with inflammation

In order to respond to infections and injuries and preserve tissue homeostasis, immune system is essential. Brain's main immune cells, known as microglia, create substances that affect neighbouring astrocytes and neurones and constantly scan the surroundings. Under typical circumstances, microglia continue to produce neurotrophic and anti-inflammatory substances while remaining in a dormant state [4]. But when infections or tissue damage occur, they transition to an active state, which triggers a reaction of inflammation that activates immune system and starts the healing process. When the infection is eradicated or the tissue is restored, this reaction usually goes away on its own [19].

The development of tissue disease as a result of persistent inflammation indicates either the continuous existence of inflammatory triggers or the breakdown of the regular resolution mechanisms. Environmental or endogenous variables, such as protein aggregation, might provide persistent stimulation that the immune system interprets as dangerous signals. Normal resolution processes can be overpowered by inflammatory reactions that produce feed-forward loops. Unchecked inflammation can produce chemicals that worsen underlying disease conditions, even while some inflammatory stimuli are helpful in removing debris and repairing tissue.

Alzheimer's Disease

One of the most common age-related neurodegenerative diseases is Alzheimer's disease (AD). distressing almost 7% of individuals over age of sixty-five and about 40% of those over age of eighty in industrialised nations. The signs and symptoms of AD include memory loss, increasing cognitive deterioration, and numerous behavioural and neuro-psychiatric issuesIntracellular neurofibrillary tangles (NFTs) and extracellular amyloid plaques, made of aggregated and broken-down amyloid precursor protein (APP) components, are the hallmark clinical features of the illness. NFTs are formed by hyperphosphorylated tau protein.

An inflammatory response is indicated by astrocytes becoming more numerous, larger, and motile surrounding senile plaques (astrogliosis), and by changes in the geomorphology of microglia from a ramified (resting) to an amoeboid (active) state. In the microglia nearby the plaques, you can see positive staining of proinflammatory mediators such MHC class II, Cox-2, MCP-1, TNF-α, IL-1β, and IL-6, along with activation signs. By stimulating chemotaxis, MCP-1 facilitates the recruitment of astrocytes in the vicinity of senile plaques. Additionally, it has been observed that post-mortem AD brains have higher amounts of chemokines and cytokines, as well as their receptors, such as IL-1α, CXCR2, CCR3, CCR5, and TGF-β [20].

Traumatic damage may cause sustainable inflammatory responses inside brain by activating astrocytes and microglia. Numerous environmental variables can affect inflammatory reactions that will participate AD pathophysiology, such as acute injury, systemic infection, and nutrition. The immune system's innate mechanisms might include activated with infection in the initial phases of AD development [21].

Type 2 diabetes with AD have recently been found to be strongly correlated. Type 2 diabetes, which is typified by hyperinsulinemia, raises the menace of AD in older individuals. The brain may be directly impacted by systemic inflammation that leads to insulin resistance, or tissue macrophage activation in type 2 diabetes may be a replication of a mutual underlying microglial dysfunction, which also independently activate inside the CNS [22].
Regarding pathology that is dependent on

inflammation, the production of amyloid beta (Ab) and accompanying tauopathy appears in adequate as shown in studies of the N-APP/DR6 mouse model of Alzheimer's disease, to be sufficient to trigger a cell-mediated stress neuronal response. on the N-APP/DR6 mice model of Alzheimer's disease [23]. However, through the TLR and RAGE pathway, Ab aggregates and dead cell products can activate astrocytes and microglia, causing local inflammation and neuronal death. The functions of Ab and other putative inflammation initiators are unidentified, however inflammatory amplifiers like IL1b, TNF alpha, and IL6 are synthesised when caspases and transcription factors like NF-kB and AP-1 are activated. These cytokines that promote inflammation can cause death in neurones and lead to increased Ab production, hence stimulating microglia-mediated inflammation [24], [25], [26].

The creation of neurotoxic chemicals that supports the development of AD may be increased by the interaction between neurones and glia. Most likely, the receptor types expressed within different neuronal populations determine region-specific effects on neurones. For instance, TNF-a promotes cell survival and death by binding to TNFR1 and initiating the NF-kB and caspase signalling pathways. TNFRII signalling, on the other hand, only stimulates NF-kB. The key targets of neurotoxic processes are still unclear, despite the fact that neuronal damage is the cause of Alzheimer's disease symptoms. New researchers are indicating that neurones like glutaminergic and GABAergic, may also be imperative targets of AD pathogenesis, which was previously thought to be main cause of cholinergic neurones loss in the basal forebrain [27].

Parkinson Disease

Motor weakness and neuropsychiatric symptoms are hallmarks of Parkinson's Disease (PD), a common neurodegenerative disease of the central nervous system. Important features of Parkinson's disease include the formation of Lewy bodies and neurites and the loss of dopamine-mediated neuronal production in the substantia nigra, a brain area critical for motor control. Within neurones, alpha-synuclein clumps together to create Lewy bodies and neurites [27]. Although, the precise origin of Parkinson's disease is still unknown, theories include poor protein clearance, neuroinflammation, and mitochondrial abnormalities.

The activation of monocytes and microglia in against misfolded alpha-synuclein causes neuroinflammation in PD [28]. Blood brain barrier (BBB) is found to be broken by the proinflammatory as well as neurotoxic cytokines and chemokines unrestricted by these immune cells, which allow lymphocytes to enter the injured area [28]. Many studies rely on the 1-methyl-4- phenyl- 1, 2, 3, 6- tetrahydropyridine (MPTP) mouse model of PD, which uses toxin to induce dopaminergic neurone death parallel to that seen in PD, even though the character of immune system is clear from blood and post-mortem brain samples as well as from the efficacy of treatments [29].

The number of lymphocytes in the peripheral and central nervous systems is debatable, although universal inflammation raises risk of PD [30]. According to some research, PD patients' peripheral blood contains fewer T and B lymphocytes [31], but other studies reveal that their blood and cerebrospinal fluid (CSF) contain higher concentrations of autoantibodies specific to alpha-synuclein [32]. The decrease in B lymphocytes is related with modifications in B cell-related gene expression in PD patients' marginal blood leukocytes [33]. However, it is still unknown if these alterations are due to CNS damage or cause it [34].

Lymphocytes are also involved in dopaminergic neurone loss, with evidence suggesting an autoimmune character of T-lymphocytes in PD, as patient-derived T cells recognise alpha-synuclein in pre-clinical and initial PD patients [35]. Neuroinflammation in PD is pathogenic through inhibition of the JAK/STAT pathway, vital for immunological modulation [36].

Several MPTP models have been used to illustrate how adaptive immune system subsidizes to pathophysiology of PD. The antiviral oral medication Maraviroc decreased T lymphocyte infiltration into the CNS in an MPTP monkey model of PD, preventing nigrostriatum neuronal cell death and enhancing motor performance [37].

Th17-cells and also cytokine IL17 also connected to PD. Animals immunised with nitrated alpha-synuclein in the MPTP paradigm develop a response of adaptive immunity. Neuroinflammation and neurodegeneration were made worse by the adaptive transmission of immune cells as of immunised mice and into recipients before MPTP treatment, mainly through Th17 cells [37]. CD4 T cells isolated from immunised mice exhibited a Th17/Th1 phenotype shift, producing pro-inflammatory and neurotoxic cytokines like IL-17, TNF-a, and IFN-g [38]. Increased neuronal cell death associated to T cell-derived IL-17 was seen in autologous co-cultures of iPSC-derived midbrain neurones with activated T cell-derived IL-17 production, lending more credence to the involvement of IL-17 in the pathophysiology of PD.

On the other hand, Tregs shows a major role of the adaptive immune system's ability to regenerate in PD. In response to neurotoxicity, mice immunised with copolymer 1 (Cop-1) to produce non-encephalitic, MBP-specific T lymphocytes are

shielded against neurodegeneration. [39]. Additionally, animals receiving MPTP were shielded against dopaminergic neuronal cell death by adoptively transferring splenocytes from Cop-1-immunized. Since T cell-depleted splenocyte transfer has no protective effect, this protection is mediated by donor T lymphocyte infiltration to the injury site [40]. In order to promote neuroprotection, T lymphocytes secrete IL-4 as well as IL-10, which inhibit activation of microglial which causes astrocytic mediated synthesis of glial cell-derived neurotrophic factor (GDNF) [41]. Adoptive transmission of triggered Tregs after MPTP introduction caused in over 90% existence of dopaminergic neurones, but effector T cell transfer had less effect. By controlling neuroinflammation, boosting neurotrophic synthesis, and inhibiting microglial reactions to stimuli, such as aggregated alpha-synuclein, Treg-mediated neuroprotection is accomplished. This was further supported in-vitro, where co-cultures of microglia stimulated by T-cell subsets and also alpha-synuclein show that Tregs regulate the initiation of NF-kB and the reactive oxygen species produced by microglia. Effector T cells, on the other hand, increase microglial inflammation and neurotoxicity [42].

Age, which is a major risk factor for PD, just as it is for AD, with older beginning associated with more severe disease and disability [43]. Ageing causes a decline in alpha-synuclein and total tau levels in cerebrospinal fluid [44], an increase in motor dysfunction, and dopamine-related problems [45]. With conjecture centred on the impact of ageing on cell counts and signalling, the precise processes of disease development and severity remain unknown. Although Treg numbers rise with age, there is no discernible difference in overall Treg numbers or functioning between old PD patients and healthy persons [46]. The Wnt/b catenin pathway, crucial for the development of dopaminergic neurones, is downregulated as a result of neurotoxin acquaintance in PD, which intensifies neuroinflammation and oxidative stress observed in usual ageing [47].The finding were suggested that age relation with PD pathogenesis may also be exacerbated with immunological alterations in older people.

Amyotrophic Lateral Sclerosis (ALS)

ALS is common neurodegenerative illness of CNS. ALS is primarily characterised through motor dysfunction, including stiffness, muscular weakness, and difficulties swallowing [48]. Motor neurone degeneration brought on by ALS leads to advanced muscle weakness and eventually paralysis [49]. Respiratory failure or death are common outcomes of this illness. It primarily affects both upper and lower motor neurones, resulting in motor symptoms. However, recent studies show that nonmotor symptoms, like cognitive as well as behavioural abnormalities, were also present in ALS patients and are similar to those seen in frontotemporal dementia (FTD) [50]. While precise pathophysiological mechanism for ALS remains unclear, protein accumulation in motor neurones and nearby oligodendrocytes is one of disease's defining characteristics. Most ALS patients have TAR DNA-binding protein 43 (TDP-43), the primary component of these aggregates (51). SOD1 and fused in sarcoma (FUS) are two other misfolded proteins seen in certain ALS subtypes. Similar to other neurodegenerative illnesses, ALS is one of the most common between the ages of 75 and 79, and getting older is a foremost risk factor for the condition [51]. Despite adaptive immunity not being the primary pathogenic mechanism, T cells that promote inflammation have a part in the beginning of and severity of ALS. T lymphocyte infiltration has been seen in post-mortem spinal cord examinations of ALS patients [52]. Despite differences within particular T cell subsets, studies examining the immune cell profiles in the blood of ALS patients and healthy controls reveal no difference in total lymphocyte counts or CD3 T cells [53]. ALS patients have significantly lower CD4 T cell counts, but CD8 T cell counts are either unchanged or elevated. A higher percentage of CD4 T cells despite the decreasing ratio of CD4-CD8 T cells. Despite a reduction of Th2 cells and Tregs, ALS patients had higher levels of IL-13-producing CD4 T cells, a Th2 cytokine, which is correlated with the severity of the disease [54], [55]. Only the ALS twin's peripheral blood mononuclear cell (PBMC) supernatant was detrimental to rat cortical neurones, according to a study of PBMCs from monozygotic twins, one of whom had ALS and the other was healthy. The SOD1G93A mouse model, which generates human SOD1 transgene with G93A mutation that results for motor neurone degeneration and paralysis, has been used to investigate the character of the adaptive immune system in ALS [56]. The above theory states that CD8 T lymphocytes contribute to motor neurone mortality following protein.

Researchers claims that B lymphocyte numbers are unaltered in ALS patients and that postmortem of spinal cord tissue displays higher T lymphocyte infiltration but not B lymphocytes [57]. B lymphocytes have no appreciable impact on the aetiology of ALS since B cell-deficient SOD1G93A mice have survival rates and motor dysfunctions that are similar to controls, and their B cells phenotypically match wild-type B cells. Peripheral blood immunoglobulin levels in ALS patients are similar to those in healthy controls [58]. However, a unique glycosylation (A2BG2) on the IgG antibodies in ALS patients has been connected with ALS pathogenesis and development. In the last stages of the disease, these antibodies identify antigens on

motor neurones, which results in neurodegeneration [59].

Despite ALS patients' pro-inflammatory immune profiles and correlations with the severity of the disease, CD4 T cells provide neuroprotection and regeneration. ALS rats without functional T cells show reduced insulin like growth factor (IGF-1) levels, reduced microglia reactivity, as well as accelerate disease progression [60], [61]. It has been reported that SOD1G93A mice lacking functional CD4+ T cells show decreased gliosis, elevated pro-inflammatory markers, accelerated loss of motor neurones, and decreased glial glutamate transporters and trophic factors, suggesting that CD4+ T cells specifically mediate this protective function. Restitution with CD4+ T cells prolong life by fostering microglial neuroprotection [60].

SOD1G93A mice have an altered immunological profile, similar to that of ALS patients, with malfunctioning T cells and reduced lymphoid numbers [62]. As the illness progresses, Tregs also decline [63]. Unlike naïve T cell transfer, adoptive transfer of activated Tregs or effector T cells to SOD1G93A mice prolongs longevity and avoids the loss of motor function [62]. Strangely, effector T cells postpone late-phase progression while Tregs postpone the onset of neurological symptoms [62], suggesting that T lymphocyte activities vary depending on the stage of sickness. Early-stage Treg transfer from SOD1G93A mice to lymphocyte-deficient SOD1G93A mice prolongs survival via boosting IL-4 levels and modifying microglia [63]. By promoting neuroprotection, lowering astrocytic and microglial reactivity, and raising neurotrophic factors, stimulating Treg expansion in the SOD1G93A model delays the progression of the disease and extends longevity [64].

Patients with ALS exhibit lower Tregs and a pro-inflammatory phenotype [65]. Tregs decline as the disease progresses, according to several studies [63], [64]. A lower number of Tregs is predictive of more severe disease sequence and a shorter existence rate. These findings suggest that while Tregs protect or regenerate early in the disease, their number or function subsequently decreases, allowing the disease to progress. Tregs in ALS patients are dysfunctional; they limit T cell proliferation less successfully than in healthy controls, and they are more dysfunctional in patients whose ALS is progressing more rapidly. A potential therapeutic target for autologous Treg transplants to stop the progression of ALS through neuroprotection or neuro-regeneration is suggested by the restoration of suppressive capabilities by in vitro multiplication of identified ALS Tregs [57].

DISCUSSION

Neuroinflammation is key role in the development of neurodegenerative illnesses like Alzheimer's disease (AD), Parkinson's disease (PD), and amyotrophic lateral sclerosis (ALS). These conditions involve the progressive diminish of neurons in the CNS, leads to significant cognitive as well as physical impairments. The initiation of glial cells, including microglia as well as astrocytes, is vital for CNS well-being and responding to injuries, but persistent activation can result in harmful chronic inflammation. This primes to incessant release of pro-inflammatory cytokines, exacerbating neuronal damage and cell death. Misfolded proteins, like as amyloid-beta in AD, alpha-synuclein in PD, and TDP-43 in ALS, initiate these inflammatory responses, contributing to oxidative stress, mitochondrial dysfunction, and disrupted neural transmission. Persistent neuroinflammation is a major factor responsible for generation of neurodegenerative diseases, but effectiveness of blocking these inflammatory responses remains uncertain. Systemic conditions like type 2 diabetes and environmental factors such as infections and trauma further influence these inflammatory pathways. In AD, hallmark features like amyloid plaques and neurofibrillary tangles trigger a robust inflammatory response, while in PD, neuroinflammation, alongside immune system alterations, exacerbates dopaminergic neuron loss. In ALS, despite adaptive immunity not being the primary driver, pro-inflammatory T cells significantly impact disease progression. Comprehending these mechanisms is essential for developing therapeutic approaches to reduce neuroinflammation and guard neurons, potentially slowing disease progression and improving patient outcomes.

CONCLUSION

Neuroinflammation plays a critical role in the development and progression of neurodegenerative illnesses such as Alzheimer's disease (AD), Parkinson's disease (PD), and amyotrophic lateral sclerosis (ALS). Persistent initiation of glial cells, including microglia and astrocytes, leads to harmful chronic inflammation, which exacerbates neuronal damage and cell death. Misfolded proteins like amyloid-beta, alpha-synuclein, and TAR DNA-binding protein 43 (TDP-43) trigger these inflammatory responses, contributing to oxidative stress and mitochondrial dysfunction. Although the effectiveness of blocking chronic inflammatory responses in slowing disease progression remains uncertain, it is clear that systemic conditions and environmental factors influence these pathways. Understanding the underlying mechanisms of neuroinflammation is critical for developing therapeutic approaches aimed at reducing inflammation and protecting neurons, which may potentially slow down the disease progression and

also improve patient results in neurodegenerative disorders.

Declarations

A statement for conflict of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Contribution of Authors

AKT, SHD and SV are involved writing the article. PR, RK, KSY, and MS have formatted the paper with the help of SHD. AKT and MP find reviewed the paper and make it available to communicate. All author has equal contribution regarding the article.

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