

# Effect and Disease Indicative Role of Inflammation in Neurodegenerative Pathology: A Mechanistic Crosstalk of Promise and Dilemma

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## Abstract

The pathobiology of neuronal cell loss due to various endogenous or exogenous influences is clinically termed as neurodegeneration. Neurodegeneration has been reported to be the major contributor to aging and central nervous system diseases. Apart from aging and endogenous involvement, neurodegeneration also has been reported from viral infection and prion diseases. Studies have shown that, chronic degeneration of neuronal cells initiate the pathology of Alzheimer's disease-the most prevalent neurodegenerative disorder in the world. Similar neurodegenerative pathology is also evident in Parkinson's disease, multiple sclerosis, and Amyotrophic Lateral Sclerosis. Neurodegeneration negatively affects the mental and physical functioning of the patient. Intriguingly, the involvement of inflammation has been linked as the most crucial entity in the mechanistic progress of neurodegeneration. Moreover, recent data also have shown that inflammatory biomarkers can prognosticate the silent progress of neurodegeneration through low-cost diagnostic approach. Mainly, Th17 and MDSCs are the particular immune cells, which have been reported to assist adequately to get a detailed insight into the underlying pathological process in neurodegeneration. Similarly, depression and dementia are also having a crucial association with pro-inflammatory cytokines, which in chronic spectrum indicates the degenerative pathology. Together, available literatures are depicting a direct association between neuroinflammation and neurodegeneration. In the present review, we have summed up all the neuropathologies in light of inflammation and emphasized the possible diagnostic measures by using inflammatory cells and mediators as biomarkers for neurodegenerative diseases.

## Keywords:

Neuroinflammation, Neurodegeneration, Inflammatory mediators, MDSC, Th17

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**Abbreviations:**

AD: Alzheimer's Disease; PD: Parkinson's Disease; MS: Multiple Sclerosis; ALS: Amyotrophic Lateral Sclerosis; HD: Huntington's Disease; HTT: Huntingtin Gene; BBB: Blood Brain Barrier; CNS: Central Nervous System; SVD: Cerebral Small Vessel Disease; CRP: C-Reactive Protein; IL-6: Interleukin-6; IL-4: Interleukin-4; IL-1 $\beta$ : Interleukin-1 Beta; DM: Diabetes Mellitus; CVD: Cardiovascular Disorders; MDD: Major Depressive Disorder; CCR5+: CC Chemokine Receptor 5; HIV: Human Immunodeficiency Virus; LPS: Lipopolysaccharide; A $\beta$ : Amyloid-Beta Peptides; SPs: Senile Plaques; RAGE: Receptor For Advanced Glycooxidation End-Products; NLR: Nod Like Receptor; NALP3: NACHT, LRR And PYD Domains-Containing Protein 3; MHC: Major Histocompatibility Complex; Cox-2: Cyclooxygenase-2; MCP-1: Monocyte Chemoattractant Protein 1; TNF- $\alpha$ : Tumor Necrosis Factor- $\alpha$ ; ApoE4: Apolipoprotein E4; TREM2: Triggering Receptors Expressed On Myeloid Cells 2; PET: Positron Emission Tomography; MPTP: 1-Methyl-4-Phenyl-1,2,3,6-Tetrahydropyridine; SNpc: Substantia Nigra Par Compacta; ATP: Adenosine Triphosphate; PTEN: Phosphatase And Tensin Homolog; PARK 7: Parkinson Disease Protein 7; IFN- $\gamma$ : Interferon- $\gamma$ ; IGF-1: Insulin Like Growth Factors 1; SOD1: Superoxide Dismutase 1; TDP43: TAR DNA-Binding Protein 43; GJ: Gap Japs; MBP: Myelin Basic Protein; HBV: Hepatitis B Virus; TGF- $\beta$ : Transforming Growth Factor- $\beta$ ; ROR $\gamma$ t: Retinoic Acid Receptors-Related Orphan Receptor  $\gamma$ t; Th17: T Helper 17; IFN- $\gamma$ : Interferon Gamma; MDSCs: Myeloid-Derived Suppressor Cells

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**Introduction**

Neuronal cell loss has been reported to be the major cause underlying behavioural and psychological abnormalities [1-3]. It has been shown that, neurodegeneration is more frequent in aged persons but, the pathological incidences of neurodegeneration can occur regardless of age barrier [4]. Despite rigorous research and study, the actual cause and underlying molecular mechanisms of neurodegeneration seems to be equivocal. Globally, Alzheimer's disease (AD), Parkinson's disease (PD), multiple sclerosis (MS), Amyotrophic lateral sclerosis (ALS) are among most common pathological outcomes of neurodegeneration [5-8]. Besides age and

endogenous influences, neurodegeneration also have been shown to be caused by viral or parasitic infections [9]. However, the scenario of neurodegeneration differs from disease to disease depending upon the mode of infection or brain tissue damage. Blood brain barrier (BBB) disruption and destruction of myelin sheath is a common feature of MS, where such anomalies results in axon terminal damage, gliosis, lymphocyte infiltration and chronic inflammation [10]. The pathological alteration in MS precipitates into physiological anomalies like neuropathic pain, paralysis, muscle spasms and optic neuritis [11]. The pathobiology of MS indicates a clear influence of inflammation; the same is also evident in any viral infection or immune-mediated disorders that affect central nervous system (CNS) [10,12]. It is notable that, such inflammatory responses play a crucial role in health and disorders of human beings regardless of age and regulate the well-being of life support systems. The basic function of inflammatory cells like microglia is to supervise the ambient microenvironment containing glia and neurons [13]. Whenever there is any questionable particle or damage in CNS, inflammatory responses starts to communicate the supporting system to control the damage and initiate the tissue repair mechanisms [14,15]. Unfortunately, inflammatory mechanisms also promote the production of toxic entities, which not only amplify the disease tenure but also drag the fate of life support system into grave danger [16,17]. Similar mechanistic failure has been reported in neurodegenerative disorders, where inflammatory responses in chronic spectrum initiates abnormal production of inflammatory mediators like cytokines and interleukins [18,19]. AD, PD, MS, ALS and other psychological anomalies have been frequently reported with inflammatory dysregulation, which further has mechanistically been linked with proteopathy, mitochondrial dysfunction, aberrant cellular transport and cell death [20-23]. However, it is noteworthy that, chronic spectrum of inflammation with or without other disease risk factors (like oxidative stress, infection, cellular damage, necrosis) can drastically alter the fate of neuronal environment and even can cause neuronal cell loss [24,25]. Inflammation alone is less potent for neurodegeneration in AD, MS, PD and ALS. Moreover, peripheral expressions of inflammatory cells and mediators have been found to be a potential diagnostic tool for the neurodegeneration [26]. Together, role of

## Effect and Disease Indicative Role of Inflammation in Neurodegenerative Pathology: A Mechanistic Crosstalk of Promise and Dilemma

inflammation in neurodegenerative pathology is truly dual-faced [26-28]. In one hand, it is influencing the degenerative pathology; on the other hand, it promises to be a biomarker to indicate the status of neurodegeneration and assists to prognosticate the therapeutic measures. Such cross-talk could enrich the therapeutic knowledge for neurodegenerative diseases. Research and study on the particular role of inflammation in neurodegenerative disease pathology is the urgent need of time. Keeping such rationale in mind, present review intended to present all the putative roles of inflammation in CNS disorders and discussed the possible disease indicative potency for future therapeutics.

### Neuroinflammation and Neurodegenerative Disease Pathologies

#### ■ Atherosclerosis, dementia and lifestyle disorders

Atherosclerosis is a major factor in several CNS and stroke characterised diseases where vascular inflammation is witnessed as a result of rise in IL-6 levels accompanied by the movement of monocytes into damaged vascular wall following subsequent intracranial large artery stenosis progression [29]. The C-reactive protein (CRP) serves as an inflammation marker in cardiovascular diseases (CVD) predicting hemorrhage progression and atherosclerosis in the event of a stroke. In case of cardiovascular diseases, diabetes mellitus, and stroke, low-grade inflammation causes severe pathological complications [30]. In such diseases, the inflammation caused, is attributed to adipose tissue dysfunction as seen in case of hypertension and obesity [29-32]. Micro-vascular, macro-vascular, and sensory neuropathic complications at times lead to fatal consequences. Warning signs like foot ulcers are observed during a heart attack. Unhealthy food habits often lead to disorders like CVD, hypertension, stroke, metabolic syndromes, and a series of related diseases characterised by metaflammation [33].

Hypertension, depression, diabetes, dementia and cerebral strokes are notable among common lifestyle disorders, which are found to be associated with inflammation at cellular and molecular levels [34,35]. Rather than exhibiting symptoms, neuroinflammation has been reported to act silently through a distinct mechanism, believed to be associated with the development of dementia along with functional impairment in older people [36]. Risk of stroke escalates on

account of oligodendrocyte death accompanied by constant myelinated fiber degeneration; a phenomenon caused due to inflammation in the CNS which induces cerebral small vessel disorder (SVD) or better known as vascular dementia [37].

#### ■ Depression

The aging process in living beings is associated with increased expression levels of inflammatory factors similar to pro-inflammatory cytokines [38]. It is observed initially as a chronic activation of both perivascular and parenchymal microglia that produce these pro-inflammatory cytokines alongside an increased astrocytes number in brain. Such pro-inflammatory signals produced by these cytokines increases vulnerability towards quite a few neuropsychiatric diseases [15]. Experimental studies revealed elevated levels of pro-inflammatory markers like adipokines, IL-6, and CRP in overweight females which correlated to symptoms of depression and anxiety [39]. Following surgical removal of adipose tissue from the body, anxiety is observed accompanied by reduced inflammation. Patients suffering from major depressive behaviour show greater susceptibility towards diseases such as depression, cognitive dysfunction and dementia; moreover, immune, cardiovascular, cerebrovascular, and neuroendocrine systems are affected alongside the occurrence of metabolic diseases like hypertension, obesity, ageing, etc. [40,41]. Conventional antidepressant therapy not only fails to show therapeutic effects in depression but also results in treatment resistance. Reports in this regard, consider elevated IL-6 and IL-8 levels, endothelial nitric oxide synthase uncoupling, hyperglutamatergia, and oxidative stress as the primary mechanism behind inflammation. Major depressive disorders (MDD), is a severe neurological disorder associated with elevated levels of inflammatory markers like chemokines, cytokines and acute phase proteins alongside neurovascular dysfunction [14,34,36].

#### ■ Infections

On several occasions dynamic inflammatory responses are observed in CNS, viral and prion infections are crucial among such kinds. Soon after the CNS is invaded by virus, two hypothetical mechanisms are believed to activate which are, neuronal retrograde dissemination and hematogenous dissemination, through which pathogen reach the brain by traversing the BBB [42,43]. Virus can replicate in macrophage and CC chemokine receptor 5 (CCR5+) T cells

in the CNS region during developmental stages and assists in the progression of dementia [44]. As evident in case of human immunodeficiency virus (HIV), the protein gp120 and Tat has been reported to induce neuronal death by enhancing CXCR4-PKC, thereby causing neuronal dysfunction through interruption of miRNA expression [45]. HIV infection and other viral disorders are associated with rise in cytokines, cholesterol, and lipopolysaccharide (LPS) levels. The same infection is also found to be co-occurring in insulin resistance and testosterone deficiency related pathobiology [46], which are also having influential role in inflammation in the CNS [47]. Inflammatory responses trigger tissue damage and are believed to be associated with different age related diseases [38].

#### ■ Alzheimer's disease

AD is characterised by symptoms like impaired cognition, behavioral and neuropsychiatric disturbances and memory loss. For over two decades, structural changes in AD have attracted attention throughout the globe [19,48]. Amyloid  $\beta$  ( $A\beta$ ) and Tau proteins found to exist as clusters in AD neurons, which is regarded as the hallmark pathological features for AD [15]. An important hypothesis in this regard is the 'amyloid hypothesis' which was framed after observing the aggregates of  $A\beta$  fragments in 'senile plaques' (SPs) of AD brain [49]. The hypothesis postulates that accumulation of  $A\beta$  in brain initiates a neurochemical cascade; thereby, adversely affecting the neuronal and synaptic functions and resulting into cognitive impairment [49].  $A\beta$  activates microglia, which in turn provokes the production of inflammatory mediators, involved in neuronal death [50]. Microglial activation triggers the receptor for advanced glycoxidation end-products (RAGE), which is responsible for sensing  $A\beta$  [51]. In patients with type II diabetes, increased RAGE activation is associated with greater risk of AD via activation of glial cells, which mainly mediates through Nod like receptor (NLR) family. These are expressed when  $A\beta$  oligomers and fibrils induces lysosomal damage via NACHT, LRR and PYD domains-containing protein 3 (NALP3). The NLR proteins are also a key component of signaling platforms, which detects inflammation together with participation in caspase1 dependent activation of the pro-inflammatory cytokines (IL-1 $\beta$  and IL-18) [52]. Microglial cells act on the region around senile plaques, causes increased in size, rapid multiplication and motility [19]. Activation of pro-inflammatory markers like

major histocompatibility complex (MHC) class II, IL-1 $\beta$ , IL-6, Cyclooxygenase-2 (Cox-2), Monocyte chemoattractant protein 1 (MCP-1), and tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) [53]. Many a times, onset of AD is random or late due to innate immunity caused by Apolipoprotein E4 (ApoE4). Additionally, ApoE4 is also a risk factor for AD as it triggers triggering receptors expressed on myeloid cells 2 (*TREM2*) genes. Phytochemicals with activities similar to ApoE have shown therapeutic effects on experimental models of neurodegenerative diseases [54-59].

#### ■ Parkinson's disease

Among neurodegenerative disorders, PD is one of the most predominant motor-neurodegeneration with a prevalence rate of 0.13% (globally) above 65 years of age [60]. PD causes a number of movement abnormalities and shows visible symptoms which accounts both behavioural and psychiatric. Besides, PD is also associated with autonomic function impairment due to degradation of nigrostriatal connections, which is an important component of PD pathology [61,62]. PD development is characterised on the extent of damage caused to the dopaminergic neurons of the substantia nigra, which occur through the intricate interactions between external factors and genetic susceptibility [63]. Risk of PD is linked to the increase of systemic inflammatory molecules in the midbrain region activating microglia and killing dopaminergic neurons [64]. It is now known through positron emission tomography (PET) and neuropathology studies that neurovascular dysfunction and increase in permeability of BBB are the main causes for PD risk. Inflammatory response for this disease can be seen through activation of peripheral lymphocytes or rise in serum cytokine (TNF- $\alpha$ , IL-2, and IL-6) levels [65,66]. In a murine PD model, adaptive immune response was observed, as increase in MHC-II in ventral mid brain microglia and astrocytes along with inflammatory response to 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) [67]. Experimental evidence has shown that, Aquaporin-4 (AQP4) deficiency alters the expression of nuclear factor kB (NF-kB) level and related gliosis. Basically, AQP4 controls the trend of neuroinflammation through release of pro-inflammatory cytokines and Adenosine triphosphate (ATP) through astrocytes instead of microglia activation [68]. Reports also depict that, inflammatory mediators are responsible for localised damage particularly in substantia nigra par compacta (SNpc). Neurons in this region

## Effect and Disease Indicative Role of Inflammation in Neurodegenerative Pathology: A Mechanistic Crosstalk of Promise and Dilemma

operate under high oxygen conditions resulting in reduced antioxidant glutathione and therefore are more prone to oxidative damage [69]. What follows reactive oxygen species (ROS) generation by microglia, instantly activates upon oxidative stress [6]. Hereditary PD and Phosphatase and tensin homolog (PTEN) is associated with mutation in DJ-1 or Parkinson disease protein 7 (PARK 7), loss of function of which is evident in PD patients. Mutation in DJ-1 impairs antioxidant response, which further reported to be associated with microglia activation in rodent model of PD [70]. Microglia activation can be triggered by a number of factors which include damage signals arising from toxins, endogenous protein products, by-products from neuronal death, and pathogens. Genomic studies report several pro-inflammatory factors such as IL-1 $\beta$ , TNF- $\alpha$ , IL-2, IL-6 and interferon- $\gamma$  (IFN- $\gamma$ ) that are expressed in PD patients due to such mechanism of action [65,69]. It is also reported that, pathologically altered form of  $\alpha$ -synuclein activates microglia and hampers the clearance of  $\alpha$ -synuclein, which ultimately results into inflammation-mediated neurodegeneration, neuronal dysfunction, and phagocytosis [71,72]. This process is influenced by pro-inflammatory cytokines produced by microglia triggering oxidative stress [6].

### ■ Amyotrophic lateral sclerosis

ALS is a collective degeneration of motor neurons in the brain cortex, motor cortex, and lower motor neurons in the spine [73]. Other symptoms of ALS include dysphagia, speech difficulties, and weakness in hands and/or legs [74]. Studies conducted on both animal and human subjects confirm that ALS pathogenesis is attributed to microglia [75]. Inflammation basically, serves as a key factor in course of the disease with effective involvement at two different stages i.e., initially in a protective mode, later causing neurotoxicity [76]. Experimental data from lumbar spinal cord SOD1G93A mice was compared with end stage SOD1G93A mice microglia and the result showed loss of motor neurons in end group, which revealed the direct influence of inflammation in ALS pathology [77,78]. Similar experiment also proved the involvement of interleukin-4 (IL-4) along with insulin like growth factors 1 (IGF-1), which considerably increases microglia expression [77,78]. In advanced stages of ALS, pro-inflammatory properties are observed, as rise in interleukin-1 beta (IL-1 $\beta$ ) and tumor necrosis factor  $\alpha$  (TNF- $\alpha$ ) in spinal cord [76].

ALS autopsy reports have shown the extent of microgliosis, which mainly predominant in spinal cord. PET imaging study also established the similar result of microglia activation [79]. *In vivo* studies found microgliosis in different motor regions of the brain and dorsolateral perfrontal cortex and thalamus [80]. Recent finding in transgenic mice model showed aggregation and mislocalisation of toxic protein aggregates in motor neurons, which triggers microglia and astrocytes mediated inflammatory processes [76]. Together, inflammatory process through LPS and TNF- $\alpha$  and other inflammatory mediators provide a direct link between microglia activation, neuroinflammation and ALS pathology [76]. Gap japs (GJ) play crucial role in the event of neuroinflammation. GJs are providing intercellular channels connecting cytoplasmic compartment of nearby cells letting passage of small molecules and ions upto ~1000Da [81]. GJ contains six subunits protein complex called connexins, which after mutation or during inflammation abnormally regulates hemi-channel function [82]. Moreover, chronic damage signals result in microglial activation, after which constant release of cytotoxic factors promoting neurodegeneration in motor neurons of hypothalamus subsequently leading to development of AD, ALS and PD [28,83].

### ■ Huntington's disease

Huntington's disease (HD) is an inherited autosomal dominant neurodegenerative disorder characterised by onset of motor dysfunctions, psychiatric issues along with intellectual weakening in late adulthood [84]. Post-mortem brain tissues have revealed that, microglial activation is evident in HD brain, which profoundly accounts striatum, globus pallidus, and cortex region [84]. It is also reported that, quantitative increase in activated microglia is correlated with the neurodegeneration in HD [85]. Interestingly, similar pathobiology of HD due to microglial activation is also reproducible in rodent model of HD [86]. Besides microglial activation, HD pathology is also reported with increased activity of astrocytes, which is crucial for the generation of inflammatory mediators like IL-6, IL-8, TNF- $\alpha$ , MCP-1, CCL2, and IL-10 [87,88]. However, whether the actual role of inflammation covers the HD pathology actively or reactively is a matter of further experimentation and discussion.

### ■ Multiple sclerosis

MS is an autoimmune disorder characterized

by demyelination, inflammation, and axon degeneration in the CNS. Most prevalent form of MS is the relapsing-remitting MS wherein the disease alternates between phases of inflammation, demyelination, and remission [10,12,89]. The inflammatory response in MS is caused, once T and B lymphocytes recognise the myelin basic protein (MBP) present in the myelin sheath in neurons as an auto-antigen. The perivascular region of CNS is prone to movement by antibodies and lymphocytes. These are also observed in demyelinated lesions suggesting inflammatory response [14,90]. In relapsing-remitting MS, despite remyelination take place during remission; the process remains compromised and causing severe neurodegeneration [91,92]. Among exogenous factors, viruses and bacteria are believed to be one of the most possible initiators of MS. These initiators function through molecular mimicry otherwise as self-antigens [93,94]. This is evident in case of hepatitis B virus (HBV) which encodes a protein resembling MBP in terms of epitope structure. In response to HBV, T-cells are immediately activated and cross react with the MBP present in major histocompatibility complex available on the surface of antigen presenting cells (APCs). It is indeed the cytokines secreted out of APC that triggers differentiation of T cells into effector cells [95]. Together with astrocytes, APC express toll-like receptors (TLRs) that are involved in MS. Even though the participation of TLRs in MS has long been established, the nature of TLR signaling is still unclear, whether it is disease promoting or protective [10]. However, reports indicates that, owing to transforming growth factor- $\beta$  (TGF- $\beta$ ) and IL-6 secretion, naïve T-cells differentiate into retinoic acid receptors-related orphan receptor  $\gamma$ t (ROR $\gamma$ t) expressing T helper 17 (Th17) cells, which are having immense importance in MS pathogenesis [96].

#### **Neuroinflammation and Neurodegeneration: A Tale of Promise and Dilemma**

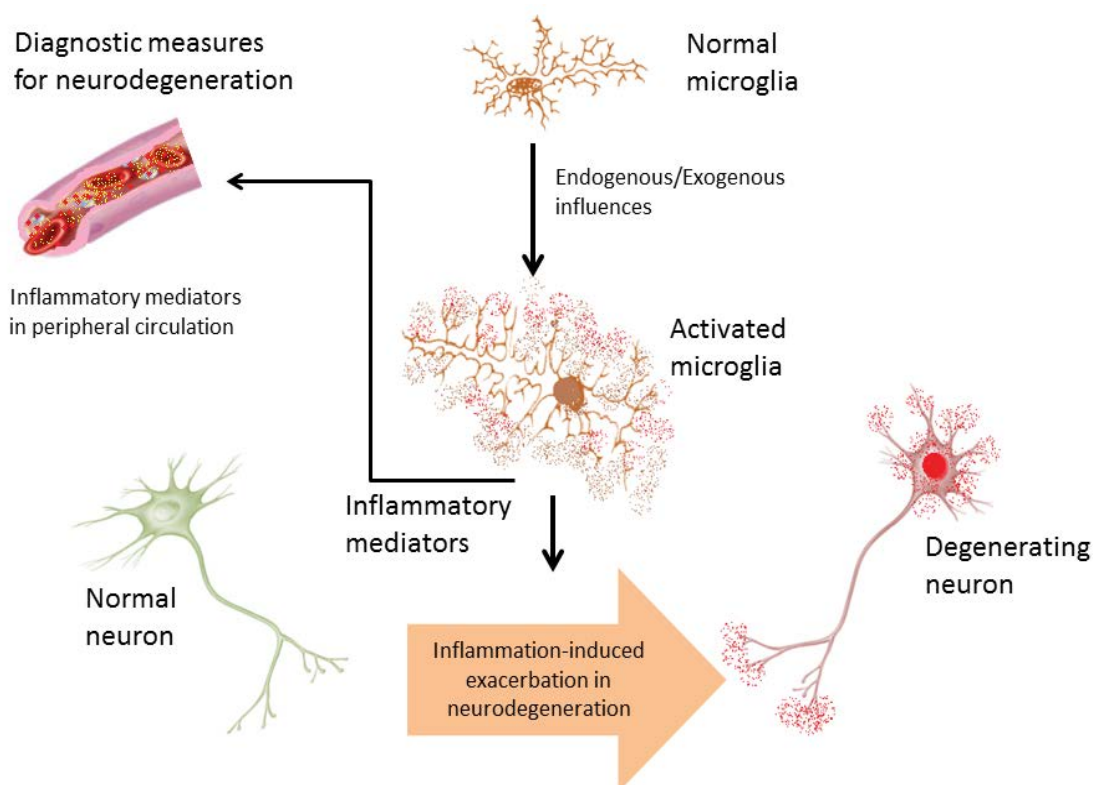
CNS remains under high surveillance and protection through innate and acquired immune responses. Both of these remain closely regulated by endogenous and exogenous influences [97]. In neuroinflammation perspective, involvement of leukocyte movement from surrounding regions into the CNS has been reported to be the crucial in the pathobiology of neurodegeneration [98,99]. Infiltration of leukocytes results in a strong inflammatory response in the peripheral organs during pathogenic invasion or systemic

LPS exposure [100,101]. As a result, microglial activation has been reported. Furthermore, pro-inflammatory mediators have been reported to release following such activation of microglia making BBB permeable [102,103]. This results in transport of peripheral leukocytes like T-cells and macrophages into the CNS. Invaded lymphocytes and macrophages share quite a few functional similarities with microglia like TLR expression, activation through aggregated proteins or pathogens, MHC class II expression, controlling T-cell phenotypes, and polarising functional phenotypes headed for an inflammatory M1 or anti-inflammatory M2 state. Thereby, influencing both inflammatory as well as lymphocyte regulatory T-cells to spread the range of inflammation throughout systemic and CNS regions [104-106]. Alteration of CD4+ and CD8+ T-cells are detected in subjects suffering from neurodegenerative disorders suggesting involvement of T-cells in such diseases apart from posing a persistent antigenic contest [10,107-109]. Presence of antibodies alongside neuronal antigen confirms role of immunity in neurodegenerative disorders [110]. An acute neuroinflammatory response is therefore considered helpful in reducing risk of damage as it activates our innate immunity. Conversely, chronic inflammation involves standby activation of microglia preventing release of inflammatory mediators causing increase oxidative stress together with nitrosative stress endless extending the inflammation cycle, which adversely affects neurodegenerative diseases [111-113]. It has been reported that, T-cells infiltrate CNS and regulate the functions of neurons and glial cell population. By doing so, T-cell marks its association in innate immune response during an inflammation or infection [114,115]. Similar mechanism with microglia activation along with existing cellular stress and chronic inflammation has significant role in the pathophysiology of neurodegenerative diseases [8,114]. In AD and ALS patients, abnormal phosphorylation of proteins has been observed and intriguingly, IL-1 positive microglia also found in such pathologies, which confers the putative role of inflammatory mediators in neurodegenerative pathology [116,117]. Moreover, it's been always consistent that, neuroinflammation accompanied with oxidative stress exerts detrimental consequence in chronic neurodegenerative disease profile. Neurotoxic species such as tumor necrosis- $\alpha$  (TNF- $\alpha$ ), glutamate, ROS and NOS play crucial role in the manifestation of such action [25].

## Effect and Disease Indicative Role of Inflammation in Neurodegenerative Pathology: A Mechanistic Crosstalk of Promise and Dilemma

With respect to the promising attributes of inflammation as disease indicator; several studies have been conducted which opens up a new avenue of therapeutics for neurodegenerative disorders [118]. In PD, it has been reported that, inflammation plays a crucial role in neurodegenerative pathologies by releasing interferon gamma (IFN- $\gamma$ ), interleukin family molecules, and cytokines in the dopaminergic center, which are also found in higher levels during disease condition [64,119]. Among various inflammatory mediators and cells Th17 and myeloid-derived suppressor cells (MDSCs) are notable in this regard [26]. Studies have shown that, Th17 cells infiltrate the region causing uncontrolled microglial activation thereby resulting in neurodegeneration [120,121]. Available reports have shown that, BBB dysfunction is the main reason behind such increased levels of inflammatory mediators in peripheral circulation [103]. Moreover, Th17 also capable of influencing the secretion of IL-17, which in turn assists increased secretion of other detrimental inflammatory factors like tumor necrosis factor alpha (TNF- $\alpha$ ) and interleukin-1 (IL-1) [122-124]. In this way Th17 spreads the inflammatory responses promptly throughout the brain by activating microglial population

[116]. On the other hand, expression of MDSCs is known to inhibit inflammation, which is quite opposite to the function of Th17 [125-127]. Though, maturation and transformation of Th17 cells are highly regulated by MDSCs, the overall increase in their peripheral levels are the determining criteria for the diagnosis of chronic inflammation [128]. Moreover, recent evidences are indicating that, MDSCs are also associated with increased inflammation by transforming CD4+ T lymphocytes into Th17 cells, which in turn increase the inflammation and promotes progressive neurodegeneration [128-130]. The development and occurrence of PD have shown a positive correlation with Th17 and MDSCs; however, the actual mechanism of action remains unknown [21]. Literature sources nevertheless confirm its involvement in early disease developmental stages; therefore, these could be considered as useful biomarkers for neurodegeneration [31,131]. More research are need to be done to get a clear insight into the mechanisms of neurodegeneration and such inflammatory mediator quantification from cerebrospinal fluid could provide better understanding on the neurodegenerative progress in various neurological diseases (**Figure 1**).



**Figure 1:** Schematic presentation of neuroinflammation in neurodegeneration.

### Conclusion

Neuroinflammation and neurodegeneration are mechanistically inseparable and exhibiting profound effects in the health and well-being of subjects. Particularly in neurodegeneration, abnormalities of the immune response components have been reported frequently. As a result inflammatory mediator molecules and cells are found in elevated levels. Due to disruption of BBB, such mediators traverse the limiting barriers and reaching the peripheral circulation. It is also reported that, both the innate and acquired immune components along with inflammatory mediators from glial cells serve as sensors for brain tissue. Therefore, peripheral quantification of such immune components

could provide an insight into the actual disease scenario in case of neurodegeneration. However, specific inflammatory mediator identification, correlative analysis and region specific quantification strategies could promise for a novel diagnostic tool for neurodegenerative pathologies. Together, neuroinflammation is having a potential to enrich the diagnostic manifestation for neurodegeneration, besides having its putative role in neurological anomalies.

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