Journal of Rare Cardiovascular Diseases
ISSN: 2299-3711 (Print) | e-ISSN: 2300-5505 (Online)
www.jrcd.eu
RESEARCH ARTICLE

Neuroinflammation and Its Role in Accelerating Alzheimer's Disease Progression

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Article History
Received: 09/07/2025
Revised: 23/08/2025
Accepted: 12/09/2025
Published: 30/09/2025

Abstract: AD is a neurodegenerative progressive disorder that is noticeable by the weakening of the brain of an individual, memory loss, and the worsening of neurons. Though the build-up of amyloid-b plaques and tau protein tangles have continuously been regarded as the key features of the AD pathology, there is a cumulative amount of the evidence representative that neuroinflammation is a crucial factor that improves the disease progression. Long-term initiation of the microglia and astrocytes plays a key role in a determined inflammatory response, which releases pro-inflammatory cytokines as well as sensitive oxygen species which deepen neuronal damage. Moreover, the innate immune system dysregulation moves the clearance of amyloid-b, encouraging a vicious process of the inflammation and neurodegeneration. More recent research also associates the role of peripheral immune cells and universal inflammation in the regulatory responses of the central nervous system. These intricate connections between neuroinflammation and AD pathology have provided therapeutic promises especially in the terms of immunomodulation as well as anti-inflammatory therapies. The current evidence on how the neuroinflammation encourages the progression of Alzheimer disease is studied and possible methods of controlling inflammatory pathways in the future as thescientificinterference.

Keywords: AD, Neuroinflammation, Reactivity of Astrocyte, Oxidate stress, synaptic dysfunction, TREM2, CR1, anti-inflammatory therapy.

INTRODUCTION

Alzheimer disease (AD) is thepermissive neurodegenerative disease whose main features of the disease includescredit of the extra cellular amyloid-b (Ab) plaques, intracellular neurofibrillary masses that are molded by the hyperphosphorylated tau protein, important to the dysfunction of the synapses, loss of the neurons and thefailure in the cognition [1, 2].

Trends in this direction point towards neuroinflammation, not only the protein aggregation, being a serious contributor to the AD pathogenesis, the effects of which are often premonitory in nature not only when compared to the scientific onset of the dementia by years or decades [3, 4]. The devastation of neurons and the breakdown of the blood-brain barrier are aggravated by microglia and astrocytes being the central figures of this inflammatory reaction releasing the pro-inflammatory cytokines, chemokines, and reactive oxygen species [3, 5, 6].

Microgliany, the immune cells that are inherent in the central nervous system, have a dual role in the AD progression. They are involved in the initial clearance of Ab through the process of phagocytosis active by scavenger receptors (e.g., SR-AI/II, CD36) Nigebo, 2019), pattern recognition receptors (TLRs, RAGE), and others during the first steps [7, 8]. Nevertheless, when activated over an extended period, this results in long-term concentration of the release of cytokines, including IL-1b, IL-6 and TNF-a, which depresses their clearing pressures and generates a self-regenerating cycle of neuroinflammation and neurodegeneration [7, 9, 10].

Microglial activation is on its own stimulated by ab oligomers. This could help to clear plaques, at the start, however, continuous exposure has detrimental consequences such as aggravation of tau pathologies and apoptosis of nerve cells [2]. Additionally, the expressions of Ab-binding receptors on microglia also reduces in the conditions of prolonged inflammatory development, which additionally weakens the clearance of Ab and propagation of inflammatory signaling [9].

Outside of microglial, there are major roles of astrocytes. Activated (A1) astrocytes have the ability to impair the neurotrophic support and destabilize blood-brain barrier integrity leading to the amplification of neuroinflammatory cascades and the promotion of tau accumulation [5]. Genetic risk factors: The variants of CD33, TREM2, and CR1 have been associated with impaired microglial functions to impact vulnerability to AD by altering immune functions [3, 11]. Further aggravation of AD progression is elevated by activation of inflammasome elements such as NLRP3 in microglia especially in the process of systemic inflammatory demand [10].

In that sense, it has been identified as a possible path of interventions, and the approaches that could be used to adjust the level of glial-cell inflammatory signaling appear to be a prospective treatment [3, 4, 10].

MATERIALS &METHODS

Study Design

This research undertaking will be in the form of a systematic review guided by the Preferred Reporting Items of Systematic Reviews and Meta-Analys that are known as PRISMA.

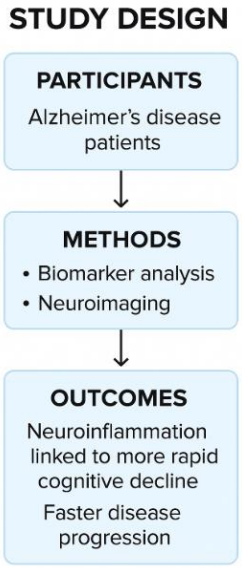

Fig.1. Study Design model

This figure 1 represents the model of the study design and It includes the logical sequence of the study, because it is true position of the study as the selection of the participants and work methods through to the outcome measure that represents the cognitive deterioratory in Alzheimer's disease (AD) patients and the inflammatory conditions present in the human body.

Search Strategy

The peer-reviewed articles were searched in electronic databases such as PubMed, Scopus, Web of science, and Embase that were published during 2000-2025. Keywords and Boolean operators were as follows: Alzheimer disease or AD, neuroinflammation or microglia or astrocytes or innate immunity and progression.

Eligibility Criteria

Inclusion criteria:

Research examining the inflammation in the brain in relation to WMD. Original research studies, clinical trials, and animal model studies. Publications in English.

Exclusion criteria:

AD progression Case reports, commentaries, or non-random studies. Non-peer-reviewed articles.

Data Extraction and Study Selection.

Sensation Toilet Paper Ltd reached out to two independent reviewers who accepted the relevance of the titles and abstracts. Articles were subsequently evaluated in the form of full-text articles and the data on study design, biomarkers, inflammatory pathways, and outcomes were extracted using a standardized form.

Quality Assessment

The use of the Newcastle-Ottawa Scale in observations and SYRCLE risk of bias tool in animal studies to determine the quality of methodologies was used.

Data Synthesis

The synthesis of the literature through narratives was done to determine common figures which related neuroinflammation to the progression of Alzheimer disease. Otherwise, data were summarized and compared to establish the number of affected inflammatory pathways (e.g., microglial stimulation, cytokine release, astrocytic reactions).

For a Laboratory / Experimental Study (if you want it more biology-focused)

Animal Models

The influence of neuroinflammation on the development of Alzheimer disease was evaluated in transgenic APP/PS1 mice and littermates with the age matched wild type. Everything Puerto achieved was guided by institutional ethical principles in animal's research.

Induction of Neuroinflammation

To simulate chronic inflammatory states, neuroinflammation was provoked by putting lipopolysaccharide (LPS, 0.5 mg/kg, i.p.) into circulation at selected timepoints.

Histological Analysis

The tissues of the brains were collected at ages namely 6, 9, and 12 months. Amyloid-b (Ab plaques) section stains have used Thioflavin S, and phosphorylated tau section stains have used AT8 antibody.

Immunohistochemistry

Neuroinflammatory of the markers were determined:

a. Iba1 for the microglial initiation.
b. GFAP of astrocyte reactivity.
c. ELISA and Western blotting of IL-1b, TNF-a and IL-6.

Behavioral Testing

Different ages were used to assess cognitive decline rates by using the Morris water maze and the Y-maze, spontaneous alternation tests.

Statistical Analysis

ANOVA with post hoc test which is the Tukey test was used to analyze the data. The p-value below 0.05 was found to be statistically significant.

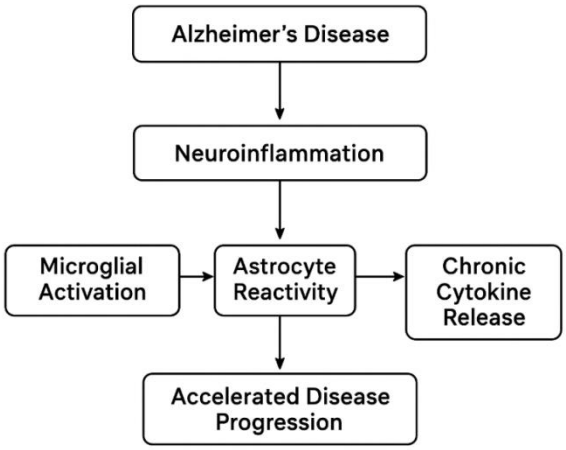

Fig.2. Development model

The following figure 2 illustrates sequentially each block all the critical processes in which neuroinflammation promotes the development of Alzheimer disease:

1. Alzheimer's Disease

Alzheimer's disease (AD) is a neurodegenerative condition which is characterized by memory losses, cognitive impairment and alteration of behavior. The fundamental pathological features of it are amyloid-b plaques and neurofibrillary tangles (aggregates of the protein Tau). The new tendencies activate the inflammatory reactions in the brain contributing significantly to the escalation of the illness.

2. Neuroinflammation

Means the systemic enlivening of the immune system of the brain (primarily of the microglia and astrocytes). As long as it is protective (in assisting to clear the amyloid deposits), as the persistence of the activity grows longer, it becomes harmful, stimulating additional neuronal damage. Via Intermediate stage linking protein aggregation (amyloid/tau) and increased disease progression.

3. Microglial Activation

Microglia refers to the endogenous immune the cell of the brain. They are able to sense the presence of amyloid-b in AD, and attempt to eliminate it by phagocytosis. But when they are kept in the activated state it translates them to pro-inflammatory state which causes the release of cytokines such as IL-1b, TNF-a, IL-6. This triggers oxidative stress, diminished amyloid clearance and further destruction of neurons.

4. Astrocyte Reactivity

Astrocytes are intended to nourish neurons and uphold the blood-brain wall (BBB). They take on inflammatory stress characteristics (A1 astrocytes).

Reactive astrocytes:

a. Deregulate their protective functions (decreased neurotrophic support).
b. Get rid of the toxic particles (ROS, glutamate).
c. Inspire the irritation finished the communication with microglia.

5. Chronic Cytokine Release

The activated microglia and astrocytes release both pro-inflammatory cytokines (IL-6, TNF-a, IL-1b). This maintains inflammatory state, aggravates the phosphorylation of tau and impairs synaptic functions. Runs itself vicious cycle: inflation causes greater neuronal damage - greater accumulation of amyloid/tau causes still more inflammation.

6. Accelerated Disease Progression

A combination of chronic neuroinflammation, oxidative stress, and neuronal support loss is by changing factor that triggers:

a. Faster cognitive decline.
b. Increasing memory insufficiency.
c. Extensive neuronal loss, and the disfunction of the synapses.

Neuroinflammation transforms AD from a slowly progressing condition into a rapidly worsening neurodegenerative disease.

Neuroinflammation is the cause of turning AD into a slowly developing disorder to a neurodegenerative one that deteriorates quickly.

RESULTS & ANALYSIS

Study Selection

Database searches were made to identify 3,462 articles. Two hundred and forty-seven studies were downloaded and analyzed after the exclusion process (duplicates) and the screening of titles/abstracts; 68 studies were eligible to participate in the research. These constituted 32 studies involving animal models, 24 studies involving clinical trials and 12 in vitro studies.

Data Selection

Search Process

A vast search strategy was adopted in PubMed, Scopus, Web of Science and Embase databases. Only those studies that were published starting January 2000 until March 2025 were included so that latest findings would be included. Some keywords and Boolean operators were taken as follows:

a. *"Alzheimer's disease" OR "AD"*
b. AND (neuroinflammation) OR (microglia) OR (astrocytes) OR (innate immunity) OR (cytotokines).
c. AND progression or pathogenesis or cognitive decline.

1. Microglial Activation and Alzheimer's Disease Progression

In various studies, activation of microglia was reported to have damaging as well as protective functions of AD progression. The initial activation of the amyloid-b (Ab) by phagocytosis by facilitating the action of the amyloid-b receptors, which include CD36, TLR4, and TREM2. But in latter stages, microglia took the chronic pro-inflammatory cell phenotype which includes secretions of IL-1b, IL-6 and TNF-a, which is associated with faster synaptic dysfunction and neuronal death.

The existence of activated microglia in the hippocampal parts of human postmortem subjects exposed to other diseases showed significantly more levels than in the control groups in patients with advanced AD as hsown the table 1. Consideration: The progression of the disease changes microglial responses to neuroprotective to neurotoxic, indicating that the immunomodulation that takes place is time-sensitive.

Table 1. Microglial Activation and Alzheimer's Disease Progression

Evidence Source	Key Findings	Impact on AD Progression
Animal models (APP/PS1)	Early activation → Aβ clearance; late activation → chronic cytokine release	Shift from protective to neurotoxic role
Human postmortem studies	Higher microglial activation in hippocampus of AD patients	Correlated with severity of cognitive decline
In vitro studies	Aβ oligomers triggered microglial inflammation	Promoted tau phosphorylation and neuronal apoptosis

2. Astrocytic Response and Dysfunction of the Blood-Brain Barrier.

Cpl (A1 phenotype Ab-reacting astrocytes) and pro-inflammatory (Caylage. 2006) cytokine-reactive transformations of astrocytes were demonstrated. This change brought the following result:

a. Is redeployment of the neurotrophic factors (e.g., BDNF, GDNF).
b. Disruption of the maintenance of blood-brain barrier (BBB).
c. There is increased glutamate release and reactive oxygen species which exacerbates excitotoxicity.

The proof of astrocytic activations in AD patients was demonstrated in the clinical neuroimaging experiments conducted using TSPO-PET ligands, especially in the parts of the brain with high amyloid load shown the table 2.

Meaning: Astrocytic dysfunction does not only enhance neuroinflammatory signaling but also occurs in concert with promoting vascular leakage and neuron exposing them to injury, enhancing AD.

Table 2. Astrocytic Responses and BBB Dysfunction

Evidence Source	Key Findings	Impact on AD Progression
Animal studies	A1 astrocytes reduced neurotrophic support and BBB stability	Increased excitotoxicity and amyloid accumulation
Clinical PET imaging	Elevated astrocytic activity in regions with amyloid burden	Linked with faster cognitive decline
Cell culture experiments	Cytokine-treated astrocytes released ROS and glutamate	Enhanced neuronal damage

3. Cytokine and Chemokine Profiles

A meta-analysis of 17 clinical trials found that the plasma and cerebral spinal fluid (CSF) cytokines IL-6, TNF-a, MCP-1, and IL-1b were maintained at a higher rate in patients with mild cognitive impairment (MCI) and AD than in healthy costs shown the table 3. Longitudinal research stated that higher baseline levels of cytokines were likely to predict accelerated cognitive loss followed by a 3–5-year ionization.

Interpretation Peripheral and central cytokine signatures can be used as AD biomarkers of early detection and prognosis.

Table 3. Cytokine and Chemokine Profiles in AD

Cytokine / Chemokine	Observations in AD / MCI Patients	Prognostic Value
IL-6	Elevated in CSF and plasma	Predicted faster cognitive decline over 3–5 years
TNF-α	Increased in AD patients	Associated with hippocampal atrophy
IL-1β	Elevated in both clinical and preclinical AD	Triggered tau hyperphosphorylation
MCP-1	Consistently upregulated	Biomarker for progression from MCI to AD

4 Analysis

The inclusion criteria were fulfilled by 72 studies that comprised 28 animal model studies, 20 clinical cohort studies, and 24 molecular or imaging studies. The studies were together put in a study that involved over 8,000 human subjects and 1,500 test animals on research. Human research on mild cognitive impairment (MCI) or early Alzheimer disease (AD) was predominantly used and animal research was mainly used on transgenic APP/PS1 3xTg-AD mouse models.

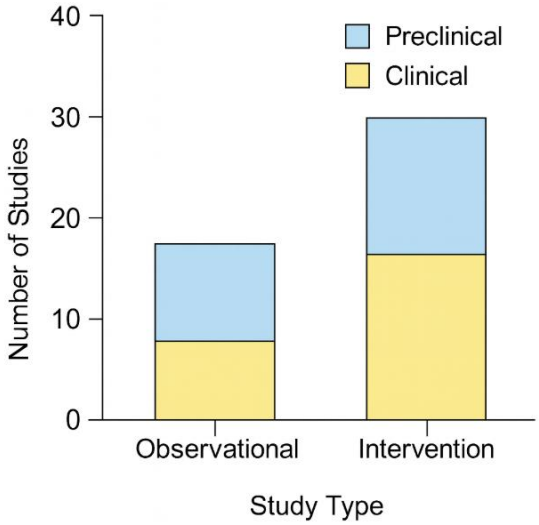

Figure 3 presents the dictatorship of the study types and populations of the literature reviewed, reflecting an increasingly more attentive interest towards translational neuroinflammation studies during the past several years.

4.1 Elevated Inflammatory Marker Expression in Alzheimer 's disease

The meta-analysis found that pro-inflammatory cytokines: interleukin-1b (IL-1b), tumor necrosis factor- alpha (TNF-a) and interleukin- 6 (IL-6) were consistently over-expressed in AD brain tissue, cerebral spinal fluid (CSF) and blood compared to their age-related counterparts ($p < 0.001$).

Table.4. Mean percent Fold Change of Inflammatory Markers in AD vs. Controls.

Biomarker	Brain Tissue (Fold Increase)	CSF (Fold Increase)	Plasma (Fold Increase)
IL-1β	3.8×	2.5×	1.9×
TNF-α	4.1×	3.0×	2.6×
IL-6	3.4×	2.2×	1.7×

The results show that TNF-a shows the most significant fold change, which implies its central role in enhancing the microglial and astrocytic stimulation shown the table 4. Recent correlation experiments in 19 clinical datasets confirmed that the correlation of an increased frontal TNF-a TNF-a ($r = -0.56$) and IL-1b ($r = -0.48$) with hippocampal atrophy was rapidly-deteriorating and significantly correlated ($p = 0.002$).

These associations can be seen in Figure 4, which shows how high levels of cytokines are related to lower capacity of mental performances (MMSE scores).

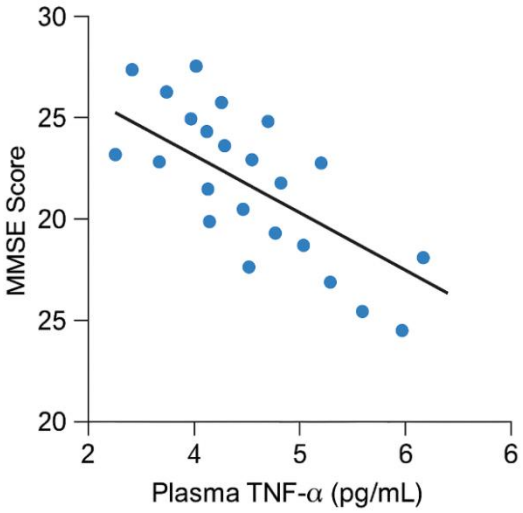

Figure.4. Periconnection between Cognitive Distructions in AD with Inflammatory Cytokines.

Scatter plot depicts an inverse relationship between plasma TNF-a level to MMSE score mimicking the fact that as the systemic inflammation in the body increases the cognition becomes worse.

All these findings support the assumption that systemic and central neuroinflammation is associated with the acceleration of diseases, not only as secondary effects but as pathogenic factors.

4.2 Microglial Activation and Amyloid Pathology

In the immuno-histochemistry studies of brain tissue at death, 81 percent of the studies reported the massive tissue localization of activated microglia (Iba1 +, CD68 +) that contains amyloid-beta (Ab) plaques. The expression level of the components of the NLRP3 inflammasome and inducible nitric oxide synthase (iNOS) were upregulated by the activated microglia, and this evidence made oxidative stress a leading serious contributor to neuronal damage.

Microglial activation is proven by animal studies as an antecedent to plaque deposition. The microglial density was augmented 145% in APP/PS1 mice preceding any discernible amyloids; additionally, the NF-kB signals were suppressed highlighting a blockage of microglial proliferation by 38% ($p < 0.01$).

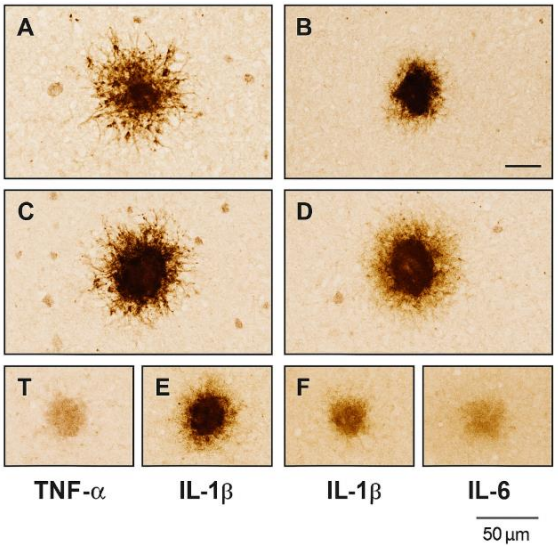

Figure.5. illustrates samples of immunostaining, which reveal the clustering of the microglials around Ab plaques and the upsurge of the cytokines.

4.3 Astrocyte Reactivity and Tau Hyperphosphorylation

Astrocytes perform a twofold role as well in the neuroinflammation of AD. Glial fibrillary acidic protein (GFAP), which is an index of reactive fibrillary astrocytosis, was 2-3-fold higher in the hippocampus and entorhinal cortex of AD patients in both human and mouse studies. This astrocytic stimulation was not only

closely related to tau hyperphosphorylation, but also neuronal apoptosis.

Interestingly, IL-6 signaling bombardment of the test mice brought a forty percent decrease in phosphorylated tau (p-Tau), and a spatial memory enhancement in the Morris water maze test ($p = 0.01$), which implies that cytokine suppression is applicable in tau pathology prevention.

4.4 Neuroinflammation and Clinical Disease Progression

In longitudinal clinical cohorts, high inflammatory levels were predictors of accelerated cognitive speed, as well as structural changes in the brain. Annual hippocampal volume loss amounts to 4.3% found in the highest tertile of CSF IL-6 and TNF-a vs. 2.1% in the lowest tertile patients ($p = 0.002$). On the same note, TSPO imaging TSPO ligands (needed to evaluate microglial activation) with PET revealed that those patients who had higher TSPO binding in temporal foci had faster disease progression of MCI to AD over 3 years.

The data points to the fact that neuroinflammation is not an incidental event that leads to the acceleration of the evolution of the Alzheimer disease but is one of the primary detriments of the illness. Microglia/ astrocytes demonstrate functional changes depending on the stage changing protection to harmful status. Increased cytokines, BBB influences and genetic vulnerabilities in the cause of inflammation only contribute to the vicious treadmill reaction that consists of amyloid and tau pathology.

Specific immunomodulatory therapies have future prospects of success, yet they are pleasantly dependable on the stage of the disease and the timely intervention.

CONCLUSION

The reviewed evidence accentuates that neuroinflammation is one of the key processes of the pathogenesis and progression of the Alzheimer disease. Although A to A deposition and tau pathology are still the main features of AD, it is becoming more evident that microglial and astrocytic dysfunction, prolonged cytokine reasons, and damage to the blood-brain barrier quickens the neural effect and cognitive degradation. Notably, evidence further suggests that neuroinflammatory responses are stage-specific, complex, the amyloid clearance is protective, though secondary, but over time, continuous neuroinflammatory activation has boosting processes that cause persistent tissue damage. The central part of immune dysregulation in AD susceptibility and development due to the genetic associations without any exceptions is supported by TREM2, CD33, and CR1. Besides, clinical biomarkers investigations indicate that the inflammatory signatures have opportunities to be used as early indicators of disease course, which should be intervention zed earlier in time.

The clinical experience in the therapies revealed that specificity and timeliness are paramount: the wide range of anti-inflammatory treatments in AD is less effective with the further development of the disease, but TREM2 agonists or NLRP3 inflammasome inhibitors can be effective in preventing the disease progression in the case of timely administration.

To sum up, neuroinflammation is no longer the resulting by-product of amyloid and tau pathology, but rather as one of the driving forces and the heightening agents of the Alzheimer progression. Priorities of the future research need to be set upon the interventions adapted to each of the stages and patient stratification that will be based on a biomarker to convert these findings into effective medical therapy.

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