

Complement system and glial activation biomarkers in cerebrospinal fluid: correlation with Alzheimer's pathology

Biomarcadores do sistema complemento e ativação glial no líquido cefalorraquidiano: correlação com a patologia de Alzheimer

Vívia Afonso Mesquita¹ , Bianca Bayma de Oliveira Arze² , Nieleenice Jerônimo de Oliveira Linhares² , Camila Soares Madeira¹ , Taiane Lima de Freitas¹ , Fernando Silva dos Santos¹ , Hamilton de Souza e Silva Júnior¹ , Adalgiza Mafra Moreno¹ , Marco Orsini¹ 

¹Postgraduate Program in Health Surveillance, Universidade Iguaçu (UNIG), Nova Iguaçu, RJ, Brazil

²Medical School, Universidade Estácio de Sá (IDOMED), Rio de Janeiro, RJ, Brazil

ABSTRACT

Introduction: Traditionally viewed through a neurocentric lens, Alzheimer's Disease (AD) has been reinterpreted considering the neuroglial unit. Microglial activation and the conversion of astrocytes to the A1 neurotoxic phenotype result in ionic imbalance and neuronal electrical silencing, culminating in synaptic opsonization via the complement system (CS).

Objective: To identify the correlation between the levels of complement system biomarkers (complement component 1q and complement component 3) and glial activation biomarkers in cerebrospinal fluid (glial fibrillary acidic protein, chitinase-3-like protein 1, and soluble triggering receptor expressed on myeloid cells 2) and cognitive performance in Alzheimer's disease.

Methodology: Integrative literature review with a mechanistic approach of articles published between 2016 and 2026, that related complement system and glial activation biomarkers in the cerebrospinal fluid (CSF) to cognitive decline in AD.

Results: Complement protein levels were associated with impoverished cognitive performance and neurodegeneration markers, while soluble fragment released in triggering receptor expressed on myeloid cells 2 (sTREM2) correlated with tau pathology markers. Glial fibrillary acidic protein (GFAP) and chitinase 3-like protein (YKL-40) showed early elevation in Aβ-positive individuals and were associated with cognitive decline and changes in cortical thickness.

Conclusion: Glial activation and complement system biomarkers may act as potential indicators of the pathophysiological dynamics of Alzheimer's disease across its clinical spectrum, reflecting early changes associated with amyloid deposition and the progression of neurodegeneration.

Keywords: Alzheimer's Disease; Complement System Proteins; Cognitive Dysfunction; Amyloid beta-peptides; Astrocytes.

RESUMO

Introdução: Tradicionalmente vista sob uma ótica neurocêntrica, a Doença de Alzheimer (DA) tem sido reinterpretada à luz da unidade neuroglial. A ativação microglial e a conversão de astrócitos para o fenótipo neurotóxico A1 resultam em desequilíbrio iônico e silenciamento elétrico neuronal, culminando na opsonização sináptica via sistema complemento (SC).

Objetivo: Identificar a correlação entre os níveis de biomarcadores do sistema complemento (componente 1q e componente 3) e de ativação glial no líquido cefalorraquidiano (proteína glial fibrilar ácida, proteína 1 semelhante à quitinase-3 e forma solúvel do receptor desencadeador expresso em células mieloides 2) e o desempenho cognitivo na doença de Alzheimer.

Metodologia: Revisão integrativa, com abordagem mecanicista, de artigos publicados entre 2016 e 2026 que relacionaram o sistema do complemento e biomarcadores de ativação glial no líquido cefalorraquidiano (LCR) ao declínio cognitivo na DA.

Resultados: Níveis de proteínas do complemento foram associados a desempenho cognitivo prejudicado e a marcadores de neurodegeneração, enquanto o fragmento solúvel liberado no receptor deflagrador em células mieloides (sTREM2) correlacionou-se com marcadores de patologia tau. A proteína glial fibrilar ácida (GFAP) e a proteína 1 semelhante à quitinase-3 (YKL-40) se elevaram precocemente em indivíduos Aβ positivos, paralelamente ao declínio cognitivo e às alterações de espessura cortical.

Conclusão: Biomarcadores de ativação glial e do sistema complemento podem atuar como potenciais indicadores da dinâmica fisiopatológica da doença de Alzheimer ao longo de seu espectro clínico, refletindo alterações precoces associadas à deposição amiloide e à progressão da neurodegeneração.

Palavras-chave: Doença de Alzheimer; Proteínas do Sistema Complemento; Disfunção Cognitiva; Peptídeos beta-amiloide; Astrócitos.

ARTICLE INFO

Received: February 12, 2026

Received in this final form: July 16, 2026

Accepted: August 10, 2026

DOI: <https://doi.org/10.46979/rbn.v62i3.72687>

CORRESPONDING AUTHOR:

Vívia Afonso Mesquita

E-mail: vivia41963@gmail.com

CONFLICT OF INTERESTS:

The authors declare no conflicts of interest.

ARTIFICIAL INTELLIGENCE

Artificial intelligence tools were used exclusively for careful grammatical and orthographic revision and to improve the clarity of the technical English language. The authors reviewed and approved the final version of the manuscript and take full responsibility for the scientific content.

FUNDING:

This study did not receive any external funding.

AUTHOR CONTRIBUTIONS (CRediT)

Mesquita VA: Study conception and design, methodology, formal analysis, investigation and original draft writing.

Orsini M: Supervision and critical review of the manuscript.

Linhares NJO & Arze BBO: Technical support in manuscript formatting, reference organization, and data collection assistance.

Madeira CS, Freitas TL, Santos FS, Silva Júnior HS, and Moreno AM: Technical collaboration and participation in supplementary data collection.

INTRODUCTION

Alzheimer's Disease (AD) is the most common form of neurodegenerative pathology, characterized by progressive cognitive decline and marked structural brain changes. AD accounts for approximately 60–70% of dementia cases worldwide. More than 55 million people are currently living with dementia globally, and nearly 10 million new cases are diagnosed each year. Given the aging population and the consequent increase in dementia prevalence, AD has established itself as a critical global public health priority.¹

Historically, neurodegeneration was interpreted through a neurocentric perspective, in which synaptic loss was considered an intrinsic and isolated event of the neuron. However, contemporary evidence has established a paradigm shift by demonstrating that neuronal viability is influenced by the immunological microenvironment and the integrity of the neuroglial unit. In this scenario, microglia act as the primary trigger for the induction of the neurotoxic phenotype of reactive astrocytes.^{2,3,4}

Elevated levels of astroglial activation markers have been associated with neurodegeneration and disease progression, indicating that the glial inflammatory response is involved in the pathophysiological processes of AD. A striking feature in this process is the presence of dystrophic neurites, containing aggregated phosphorylated tau protein (p-tau) around amyloid- β deposits.³ These neuritic dystrophies are associated with complement-mediated synaptic tagging and excessive glia-mediated synaptic elimination.^{3,5}

The Complement System

The complement system is an essential component of innate immunity, consisting of a highly regulated protein cascade that can be activated through three main pathways: classical, alternative, and lectin. These pathways converge on the activation of the central protein C3, triggering a sequence of reactions that amplify the immune response and culminate in the formation of the membrane attack complex (MAC).⁴

The classical pathway is initiated by the binding of C1q to target structures, such as immune complexes, apoptotic cells, and proteins associated with neurodegenerative processes, including fibrillar amyloid- β . The C1 complex, formed by complement component 1q (C1q) associated with the complement component 1r (C1r) and complement component 1s (C1s) proteases, initiates the calcium-dependent proteolytic cascade, promoting the sequential cleavage of subsequent components.^{4,5}

The complement system is not only widespread in the peripheral immunity but is also locally produced by microglia and astrocytes, as well as participate in physiological processes of the CNS. These processes include neuronal embryogenesis, synaptic remodeling and injury

response.⁵ In the central nervous system, complement activation occurs under strict control by regulatory proteins, which limit cascade amplification and restrict the response to specific domains.⁵

Under physiological conditions, microglia exert homeostatic functions in the central nervous system, including the removal of cellular debris and synaptic pruning—processes in which C1q activates C3 and addresses subsets of synapses for elimination. During development, C1q is preferentially deposited on less active synapses, promoting the activation of the classical complement pathway and the subsequent deposition of C3-derived fragments. These synapses are recognized by microglia through complement receptors, such as CR3, leading to their selective phagocytosis, a process essential for pruning, the refinement of neural circuits.^{5,6,7}

Similarly, early synaptic alterations observed in neurodegenerative diseases may lead to the reactivation of these physiological mechanisms. Initially, these responses may be compensatory; however, the persistence of the pathological stimulus can lead to the amplification of the inflammatory cascade, promoting excessive synaptic elimination and contributing to neurodegeneration.^{6,8}

Relationship between the Complement System, Neuroinflammation, and Cognitive Impairment in Alzheimer's Disease

In the CNS, complement system proteins are synthesized locally, playing roles that transcend innate immunity. In Alzheimer's Disease, the accumulation of amyloid- β protein induces a pro-inflammatory microenvironment, which favors the hyperphosphorylation of tau protein and consequent neurodegeneration. In this context, microglia are recruited and activated by damage-associated molecular patterns (DAMPs) in a process mediated by receptors such as TREM2. This activation modulates the secretion of critical inflammatory mediators, such as TNF- α , IL-1, and C1q, which coordinate and amplify the local neuroimmune response.⁶

In parallel, astrocytes express receptors such as Toll-like receptor 4 (TLR4) and receptor for advanced glycation end-products (RAGE), which, upon interacting with amyloid- β , activate signaling pathways such as nuclear factor kappa B (NF- κ B), promoting the expression of complement components, including complement component 3 (C3). In turn, increased C3 cleavage stimulates neuronal and microglial receptors. Neuronal activation of C3aR disrupts intracellular calcium dynamics, which is deleterious for dendritic morphology and neuronal excitability. C3 may be cleaved and generate C3a, a chemoattractant anaphylatoxin for microglia, and C3b, an opsonin that tags synapses and becomes a target for microglial phagocytosis via C1R. Once the fragment C3a activates neuronal C3aR, there is a disruption of intracellular calcium dynamics, which is deleterious for

dendritic morphology and neuronal excitability. Therefore, this mediation is associated with synaptic dysfunction and dendritic alterations. Moreover, activated microglia can induce the inflammatory A1 phenotype of reactive astrocytes. They seem less efficient in phagocytosis of both synaptosomes and myelin debris and are also known for inducing the formation of fewer and weaker synapses. In summary, astrocytes are prone to play a relevant pathological role in AD, with increased production of complement components, reduction of complement regulators, and an association with disease progression.^{9,10,11}

The reduction in the expression of complement regulatory proteins can intensify the activation of the cascade, favoring both the opsonization of synapses and the formation of the membrane attack complex (C5b-9). Although the MAC is traditionally associated with cytotoxicity, sublytic levels of this complex can exert cellular modulating effects, including calcium influx and cellular activation, depending on the intensity of the stimulus.⁶

This process corroborates neurodegeneration through two central pathways:

(1) Exacerbated synaptic elimination, orchestrated by the activation of the C1q/C3 cascade and its subsequent signaling via microglial receptors.^{5,9}

(2) A state of chronic neuroinflammation, fed back by the secretion of pro-inflammatory mediators and oxidative stress. The convergence of these factors culminates in the degradation of synaptic integrity and increased neuronal fragility.^{5,9}

These phenomena were initially evidenced in murine models. Considering that synaptic integrity is fundamental for memory and learning processes, synaptic loss represents one of the main mechanisms associated with cognitive decline in Alzheimer's disease.^{7,9}

OBJECTIVE

To identify the correlation between the levels of complement system biomarkers and glial activation biomarkers in the cerebrospinal fluid and cognitive decline in Alzheimer's disease.

METHODOLOGY

This integrative review was conducted between January and February 2026 through a structured search of the PubMed/MEDLINE and Google Scholar databases. The descriptors "Alzheimer Disease", "Cerebrospinal Fluid", "Biomarkers", "Complement System", "Glial Activation", and "Cognitive Dysfunction" were used in combination with Boolean operators (AND/OR).

Original articles and systematic reviews published between 2016 and 2026, in English or Portuguese, that investigated the relationship between complement system and glial activation biomarkers in cerebrospinal fluid (CSF) and cognitive decline in Alzheimer's disease were included.

Studies on other forms of dementia, as well as case reports and editorials not directly addressing the biomarkers of interest, were excluded.

After applying the eligibility criteria, 21 articles were included in the final analysis. Data extraction encompassed study design, evaluated biomarkers, mechanistic findings from experimental models, and reported clinical and cognitive outcomes. The synthesis of the evidence was performed descriptively, integrating findings from both experimental and human studies.

RESULTS

Table 1. Evidence of complement system and glial activation biomarkers associated with clinical outcomes in Alzheimer's disease.

Author (Year)	Study Type	Main Findings	Clinical Outcome
Wang (2024)	Clinical	Interaction between C1q and GFAP in CSF.	Transition to early stage.
Li (2024)	Longitudinal	Complement vs. brain structure.	Cognitive decline (ADNI).
Zhu (2023)	Multicenter	C1q associated with classical biomarkers.	Progressive cognitive deterioration.
DalBianco (2023)	Review	Inflammatory markers in CSF.	Aggressiveness marker.
Sjölin (2022)	Clinical	C3 levels and AD progression.	Prediction of clinical decline.
Zhang (2021)	Clinical	C3 vs. cortical atrophy and MMSE.	Correlation with brain atrophy.
Wu (2020)	Clinical	Elevated C3 in CSF.	Decline at MCI stage.
Whelan (2019)	Experimental	5-protein complement panel.	90% accuracy in progression prediction.
Morgan (2019)	Review	Complement activation in humans.	Detinant of neurodegeneration.
Leyns (2019)	Experimental	TREM2 and Tau pathology.	Barrier against neuritic plaques.
Bos (2019)	Clinical	Inflammation and synaptic degeneration.	Early-stage changes.
Dejanovic (2018)	Experimental	C1q-mediated synapse elimination.	Loss of excitatory synapses.
Liddelew (2017)	Experimental	Microglia induce neurotoxic A1 astrocytes.	Neuronal death and trophic loss.
Hakobyan (2016)	Clinical	Elevated C1q and C3 in CSF.	Prediction of MMSE decline.
Hong (2016)	Experimental	C1q and microglia in synaptic pruning.	Memory loss before plaques.
Goetzl (2016)	Experimental	Complement in neural-derived exosomes.	Peripheral blood biomarker.
Asai (2015)	Experimental	Microglia and Tau propagation via exosomes.	Pathology spreading.

Abbreviations: A1, neurotoxic A1-type reactive astrocytes; AD, Alzheimer's disease; ADNI, Alzheimer's Disease Neuroimaging Initiative; C1q/C3, complement component 1q and 3; CSF, cerebrospinal fluid; GFAP, glial fibrillary acidic protein; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination; TREM2, Triggering Receptor Expressed on Myeloid cells 2.

Evidence from Murine Model Experiments

Different lines of evidence converge on the role of neuroimmune communication in AD. A combined glial activation study established a causal link by demonstrating that microglial secretion of a specific cocktail (IL-1 α , TNF- α , and C1q) is the necessary stimulus for the induction of the A1 reactive astrocyte phenotype. In this assay, a threefold increase in GFAP expression was observed among A1 astrocytes, which is correlated with the loss of synaptic homeostatic function. The translation of these findings to human pathology was corroborated by immunohistochemical analyses of prefrontal cortex tissues, which identified the co-expression of C3 and GFAP in reactive astrocytes, validating the conservation of this glial state both in experimental and human models.¹⁰

The pathophysiology of synaptic attrition was elucidated in early-progression murine models, revealing that C1q deposition is fostered even before the amyloid plaque formation, just by the presence of oligomeric A β . In turn, the C1q is required to perpetuate the degenerative process. The aberrant C1q accumulation at the synapses signalizes downstream C3 activation. This molecular cascade was characterized through the colocalization of C1q with the postsynaptic density protein PSD-95, ultimately triggering the activation of C3.⁷

Experimental evidence in murine models provides the role of the complement system in the synaptic dysfunction, as the deletion of C1q or C3 results in significant prevention of synaptic loss ($P < 0.01$), even in the presence of amyloid deposits. These findings indicate that the activation of the complement cascade is necessary for the execution of microglia-mediated synaptic elimination the progression of neurodegeneration.⁷

Consistent results were observed in murine models of amyloidosis and tauopathy, in which the activation of the complement cascade acts as an effector mechanism of neurodegeneration, characterized by C1q-mediated synaptic opsonization and subsequent microglia-dependent synaptic elimination, with functional impact on neural circuits and cognitive performance.¹²

Accordingly, analyses of human brain tissue show increased C3 at the synapses of Alzheimer's disease patients, particularly in regions associated with tau pathology. Furthermore higher intact of C3 levels and its fractions in CSF, were significantly correlated with CSF levels of tau suggesting that the complement pathway is parallel to the pathophysiology of the disease. In particular, eliminating C3 partially rescued neurodegeneration in TauP301S mice without blocking tau pathology. This implies that complement is part of the downstream cascade by which tau mediates neurotoxicity.¹²

Evidence from Human Studies

Different cohort studies have demonstrated consistent associations between neuroinflammation biomarkers in CSF and classic markers of Alzheimer's disease, as well as cognitive and structural outcomes.

In a cohort of 210 elderly individuals without established dementia from ADNI—consisting of 125 with mild cognitive impairment and 85 cognitively normal controls followed longitudinally with annual clinical, neuropsychological, and neuroimaging assessments—global and domain-specific cognitive functions were evaluated through standardized neuropsychological batteries. The results demonstrated that complement system protein levels in the cerebrospinal fluid are associated with Alzheimer's disease pathology markers and longitudinal cognitive performance, with distinct patterns according to clinical stage, suggesting a disease-stage-dependent effect. Furthermore, neuroimaging analyses

revealed associations with regional structural changes, including ventricular expansion and reduction in medial temporal structures. It is believed that part of the complement's effect on cognition is mediated by structural brain changes.¹³

In the context of microglial activation, a prospective single-center study (2018–2020, $n = 101$) demonstrated that CSF sTREM2 levels show a significant association with tau-related neurodegeneration markers, with a positive correlation with t-tau ($r = 0.427$; $p < 0.001$) and p-tau ($r = 0.296$; $p = 0.003$), while no association with Amyloid- β was found.¹⁴

In an independent cohort encompassing individuals across the Alzheimer's disease spectrum and controls, a positive correlation was observed between age and CSF sTREM2 levels in the pooled group ($r = 0.391$; $p < 0.0001$), with higher correlation values following greater severity stage. Therefore, CSF sTREM2 levels ($p = 0.002$), were higher in the group with mild cognitive impairment due to AD (MCI-AD) compared to controls and highest among the AD dementia group, in addition to an increasing trend relative to the preclinical phase. Besides, CSF sTREM2 was associated with higher levels of T-tau ($\beta = +0.336$, $P = 0.001$) and P-tau181P ($\beta = +0.370$, $P = 0.001$). Taken together, these findings reinforce the association of sTREM2 with tau-mediated neurodegeneration processes throughout the disease continuum.^{14,15}

In a multicenter study (ADNI and CABLE), it was demonstrated that CSF neuroinflammation biomarkers, including C1q, sTREM2, and GFAP, correlate with each other already in aging, even in the absence of dementia. Accordingly, aging by itself is already an assumption for neuroinflammation. From the perspective of dementia, C1q varied significantly between disease stages, being reduced in the phase associated with amyloid-beta accumulation and increased in stages characterized by tau pathology and neurodegeneration. It endorses that C1q acts as a mediator in the transition between amyloid and tau pathology, establishing an integrated neuroinflammation axis associated with cognitive decline.¹⁶

In a predictive modeling study using machine learning, the inclusion of C3 and factor H (FH) in models based on clinical variables and classic biomarkers (age, sex, APOE $\epsilon 4$, and tau) improved discrimination performance between mild cognitive impairment and mild Alzheimer's disease in the ADNI cohort ($n = 230$; $p < 0.05$), with external validation in the Emory cohort ($n = 73$; $p = 0.014$). However, findings across studies remain heterogeneous, and there is no clear consensus regarding the diagnostic performance of C3 and FH in distinguishing disease stages. Lower levels of C3 and FH have also been associated with a higher probability of clinical progression and worse performance, interpreted by the authors as reflecting possible consumption or compartmental redistribution of these components in the context of neuroinflammation.¹⁷

In the BioFINDER-2 cohort, linear mixed-effects

model analyses demonstrated that astrocytic reactivity, assessed by GFAP, constitutes a dynamic marker of Alzheimer's disease progression. Elevated GFAP levels in both plasma ($t = -3.303$; $p = 0.001$) and CSF ($t = -2.485$; $p = 0.014$) were associated with longitudinal cognitive decline, in addition to being related to the Amyloid- β deposition rate. Serum GFAP analysis might represent an advantageous tool in terms of costs and invasiveness to identify astrocytosis and to prognosticate dementia conversion.¹⁸

In a longitudinal analysis encompassing 770 individuals, the relationship between the levels of CSF YKL-40, a glycoprotein expressed by reactive astrocytes, and cognitive decline across the Alzheimer's disease spectrum was investigated. The data revealed a robust association between YKL-40 concentrations and amyloid status, highlighting a significant interaction between clinical diagnosis and Amyloid- β positivity ($P = 0.001$). High YKL-40 levels were associated with worse cross-sectional cognitive performance on the Mini-Mental State Examination (MMSE) and a higher rate of longitudinal decline, with more pronounced effects in MCI and established dementia.¹⁹

In a two-year longitudinal study, baseline CSF levels of YKL-40 and sTREM2 were associated with structural brain changes over time, including gray matter, white matter, and mean diffusivity, even in cognitively healthy individuals. The associations were modulated by age, with higher glial markers levels correlating to higher mean diffusivity, which is usually associated with parenchyma loss, especially in AD-related regions.²⁰

Finally, in the BioFINDER cohort, YKL-40 and SMOC2 levels were elevated across the Alzheimer's disease spectrum. YKL-40 levels increased as early as the preclinical phase in amyloid- β (A β)-positive individuals ($d = 0.13$; $q = 0.007$) and remained elevated in Alzheimer's disease dementia ($d = 0.17$). Furthermore, elevated YKL-40 levels were negatively correlated with cortical thickness in regions vulnerable to neurodegeneration, suggesting an association with progressive structural brain loss.²¹

DISCUSSION

The interpretation of the results requires an integrated analysis of evidence from experimental models and clinical studies. While findings in animal models provide the necessary mechanistic support to isolate variables—such as the induction of the neurotoxic astrocytic phenotype mediated by IL-1 α , TNF- α , and C1q—human cohorts reveal the dynamic nature of this response.^{8,10,16} This transition between models indicates that the microglia-astrocyte-complement axis assumes distinct functional profiles according to the progression of the pathology and the burden of neurodegeneration biomarkers.^{1,3,5,9,17}

Regarding the complement system, the role of C1q and C3 in synaptic opsonization and microglial recruitment

represents the deregulated reactivation of a physiological pruning mechanism. The heterogeneity of CSF levels observed in the literature suggests that complement does not act as a linear marker of damage, but rather as a reflection of the glial functional state: ranging from debris clearance processes and initial neuroprotection to exacerbated synaptic elimination in advanced stages, possibly aggravated by blood-brain barrier (BBB) dysfunctions.^{12,16}

Complement System, Microglial Activation and Cognitive Decline

Longitudinal analysis of biomarkers in CSF and plasma reveals a dynamic behavior reflecting different stages of the pathophysiological cascade of Alzheimer's Disease (AD).^{16,17,18,19}

GFAP has consolidated itself as one of the most consistent indicators of early astrocytic activation, showing elevation in amyloid-beta positive individuals even in the preclinical phases of the disease. The emphasis placed on plasma GFAP levels presents superior clinical relevance since greater significance was observed in the periphery compared to the CSF GFAP levels. In this sense, it emerges as a promising biomarker for screening and predicting longitudinal cognitive decline, offering lower invasiveness and greater accessibility.¹⁸

The sTREM2 (the soluble form of Triggering Receptor Expressed on Myeloid cells 2) acts as a biomarker of microglial activation in the CNS but performs differently from GFAP in terms of time: While astrocytic reactivity precedes symptoms, CSF sTREM2 becomes more pronounced during the MCI phase. Its association is linked to neurodegeneration markers, particularly total tau (t-tau) and phosphorylated tau (p-tau), rather than a direct relationship with isolated Amyloid- β deposition.¹⁸ From a clinical perspective, sTREM2 functions as an indicator of resilience or effector capacity. Adequate levels of sTREM2 in CSF are associated with the microglia's competence in containing the spread of tau pathology and performing the clearance of cellular debris. On the other hand, dysfunction in this signaling accelerates cognitive decline, consolidating sTREM2 as a potential prognostic marker to identify the transition to stages of active neurodegeneration.^{16,18} This pattern suggests that the microglial response via TREM2 is intensified by progressive neuronal injury, reflecting an attempt at functional adaptation to cellular damage and tissue remodeling.

Chitinase-3-like 1 (YKL-40), a marker of astrocytes activation, reflects the longitudinal trajectory of the disease, showing a robust association with amyloid status ($P = 0.001$) and functional decline. The elevation of YKL-40 indicates the transition to a neurotoxic pro-inflammatory environment. From a prognostic standpoint, its measurement allows for the identification of patients with a higher propensity for rapid clinical decline, consolidating it as an essential

progression stratification tool for studies aiming to modulate the astrocytic immune response.¹⁹

Integrated analysis of the cohorts reveals that the complement system acts as a dynamic biomarker of AD progression. The apparent fluctuation in the CSF levels of these components reflects the transitions between initial protein recruitment and late regulatory failure.

Quantitative data demonstrate a biphasic dynamic for the C1q complement protein. In the early stage, where there is only evidence of amyloid pathology without tau deposition or atrophy (A+ TN-), a discrete reduction in CSF levels is observed, suggesting compartmental redistribution resulting from local consumption. This phenomenon signals the loss of basal homeostasis, where the increased demand for opsonization exceeds the available supply of C1q. In contrast, in the stage of established neurodegeneration (A+ TN+), there is a significant elevation in C1q levels ($P < 0.001$), consistent with a sustained pro-inflammatory microglial state. This increase is associated with the intensification of the innate immune response, in which C1q, in synergy with inflammatory cytokines, induces the conversion of astrocytes to the neurotoxic phenotype.¹⁶

Unlike C1q, C3 and factor H reflect the inflammatory state and the system's regulatory capacity. Predictive models demonstrate that the concomitant reduction of C3 and FH in the cerebrospinal fluid (CSF) is associated with a higher risk of clinical decline ($P = 0.014$).¹⁷ This quantitative reduction suggests a state of regulatory exhaustion, characterized by the marked consumption of FH to inactivate C3b and reduce the deposition of activated fragments on synaptic surfaces. The loss of this control facilitates synaptic elimination, as well as the progression of the cascade to the formation of the Membrane Attack Complex (MAC), promoting membrane alterations and sublytic neuronal damage.^{4,5,6,9}

The clinical relevance of this dysregulation is corroborated by its direct association with cognitive outcomes. Individuals with a high biological probability for AD [P(AD) > 50%] present greater executive impairment ($P = 0.001$) and a higher rate of longitudinal decline ($P = 0.007$). These findings suggest that the dysfunction of the complement system's regulatory mechanisms not only accompanies but potentially precedes the functional deterioration of cortical circuits.¹⁷ Therefore, the components of the complement system consolidate as a central axis in risk stratification and in determining the speed of synaptopathy progression, possessing utility as underpinning markers and also as dynamic biomarkers of progression in Alzheimer's Disease.^{16,17} However, the lack of longitudinal data limits inferences regarding the temporality of these events. At the same time, the observational nature of this studies prevents the establishment of definitive causal relationships between complement, microglial activation, and subsequent neuronal loss.

Considering contemporary evidence and the framework proposed by the National Institute on Aging–

Alzheimer's Association (NIA-AA), biomarkers such as YKL-40, GFAP, sTREM2, and complement system components are currently considered emerging markers of biological processes related to neuroinflammation and glial activation. However, the definitive translation of these markers into clinical practice remains conditional on overcoming certain challenges, such as the need for rigorous analytical standardization and the definition of universally validated cut-off points.

CONCLUSION

Alzheimer's Disease (AD) represents one of the greatest biomedical challenges of our time, with a growing socioeconomic impact in the face of accelerated global population aging. The increase in longevity imposes an urgent need for a paradigm shift, transcending the classic neurocentric view toward an integrated understanding of the neuroglial unit.

The evidence reviewed supports that neuroinflammation, mediated by the functional triad of microglia, astrocytes, and the complement system, is a critical determinant in the transition between physiological aging and the pathological progression of AD. The activation of the complement cascade (C1q/C3) emerges as the mechanistic link to synaptopathy, the primary correlate of cognitive decline. In this setting, glial biomarkers such as sTREM2, YKL-40, and GFAP show potential for the dynamic monitoring of the disease, allowing for the identification of structural and functional damage starting from the preclinical phases.

REFERENCES

1. Uddin MdS, Kabir MdT, Jalouli M, Rahman MdA, Jeandet P, Behl T, et al. Neuroinflammatory Signaling in the Pathogenesis of Alzheimer's Disease. *Curr Neuroparmacol*. 2022;20(1):126–146. doi:10.2174/1570159X19666210826130210
2. Basha SC, Ramaiah MJ, Kosagisharaf JR. Untangling the Role of TREM2 in Conjugation with Microglia in Neuronal Dysfunction: A Hypothesis on a Novel Pathway in the Pathophysiology of Alzheimer's Disease. *J Alzheimers Dis*. 2023;94(s1):S319–S333. doi:10.3233/JAD-221070.
3. Leyns CEG, Gratuze M, Narasimhan S, Jain N, Koscal LJ, Jiang H, et al. TREM2 function impedes tau seeding in neuritic plaques. *Nat Neurosci*. 2019;22(8):1217–1222. doi:10.1038/s41593-019-0433-0.
4. Ostrycharz E, Hukowska-Szematowicz B. New Insights into the Role of the Complement System in Human Viral Diseases. *Biomolecules*. 2022;12(2):226. doi:10.3390/biom12020226.
5. Negro-Demontel L, Maleki AF, Reich DS, Kemper C. The complement system in neurodegenerative and inflammatory diseases of the central nervous system. *Front Neurol*. 2024;15:1396520. doi:10.3389/fneur.2024.1396520.
6. Shinjyo N, Kagaya W, Pekna M. Interaction Between the Complement System and Infectious Agents – A Potential Mechanistic Link to Neurodegeneration and Dementia. *Front Cell Neurosci*. 2021;15:710390. doi:10.3389/fncel.2021.710390.
7. Hong S, Beja-Glasser VF, Nfonoyim BM, Frouin A, Li S, Ramakrishnan S, et al. Complement and microglia mediate early synapse loss in Alzheimer mouse models. *Science*. 2016;352(6286):712–716. doi:10.1126/science.aad8373.

8. Targa Dias Anastacio H, Matosin N, Ooi L. Neuronal hyperexcitability in Alzheimer's disease: what are the drivers behind this aberrant phenotype? *Transl Psychiatry*. 2022;12(1):257. doi:10.1038/s41398-022-02024-7.
9. Shah A, Kishore U, Shastri A. Complement System in Alzheimer's Disease. *Int J Mol Sci*. 2021;22(24):13647. doi:10.3390/ijms222413647.
10. Liddel SA, Guttenplan KA, Clarke LE, Bennett FC, Bohlen CJ, Schirmer L, et al. Neurotoxic reactive astrocytes are induced by activated microglia. *Nature*. 2017;541(7638):481–487. doi:10.1038/nature21029.
11. Lian H, Litvinchuk A, Chiang ACA, Aithmitti N, Jankowsky JL, Zheng H. Astrocyte-Microglia Cross Talk through Complement Activation Modulates Amyloid Pathology in Mouse Models of Alzheimer's Disease. *J Neurosci*. 2016;36(2):577–589. doi:10.1523/JNEUROSCI.2117-15.2016.
12. Wu T, Dejanovic B, Gandham VD, Gogineni A, Edmonds R, Schauer S, et al. Complement C3 Is Activated in Human AD Brain and Is Required for Neurodegeneration in Mouse Models of Amyloidosis and Tauopathy. *Cell Rep*. 2019;28(8):2111–2123.e6. doi:10.1016/j.celrep.2019.07.060.
13. Li M, Ma YH, Guo Y, Liu JY, Tan L, on behalf of Alzheimer's Disease Neuroimaging Initiative. Associations of cerebrospinal fluid complement proteins with Alzheimer's pathology, cognition, and brain structure in non-dementia elderly. *Alzheimers Res Ther*. 18 de janeiro de 2024;16(1):12. doi:10.1186/s13195-023-01377-5.
14. Park SH, Lee EH, Kim HJ, Jo S, Lee S, Seo SW, et al. The relationship of soluble TREM2 to other biomarkers of sporadic Alzheimer's disease. *Sci Rep*. 22 de junho de 2021;11(1):13050. doi:10.1038/s41598-021-92101-6.
15. Suárez-Calvet M, Kleinberger G, Araque Caballero MÁ, Brendel M, Rominger A, Alcolea D, et al. sTREM2 cerebrospinal fluid levels are a potential biomarker for microglia activity in early-stage Alzheimer's disease and associate with neuronal injury markers. *EMBO Mol Med*. maio de 2016;8(5):466–76. doi:10.15252/emmm.201506123.
16. Guo F, Sheng ZH, Fu Y, Wang ZB, Xue RJ, Tan L, et al. Complement C1q is associated with neuroinflammation and mediates the association between amyloid- β and tau pathology in Alzheimer's disease. *Transl Psychiatry*. 17 de julho de 2025;15(1):247. doi:10.1038/s41398-025-03458-5.
17. Hu WT, Watts KD, Tailor P, Nguyen TP, Howell JC, Lee RC, et al. CSF complement 3 and factor H are staging biomarkers in Alzheimer's disease. *Acta Neuropathol Commun*. dezembro de 2016;4(1):14. doi:10.1186/s40478-016-0277-8.
18. Pereira JB, Janelidze S, Smith R, Mattsson-Carlsson N, Palmqvist S, Teunissen CE, et al. Plasma GFAP is an early marker of amyloid- β but not tau pathology in Alzheimer's disease. *Brain*. 16 de dezembro de 2021;144(11):3505–16. doi:10.1093/brain/awab223.
19. Bos I, Vos S, Verhey F, Scheltens P, Teunissen C, Engelborghs S, et al. Cerebrospinal fluid biomarkers of neurodegeneration, synaptic integrity, and astroglial activation across the clinical Alzheimer's disease spectrum. *Alzheimers Dement*. maio de 2019;15(5):644–54. doi:10.1016/j.jalz.2019.01.004.
20. Falcon C, Monté-Rubio GC, Grau-Rivera O, Suárez-Calvet M, Sánchez-Valle R, Rami L, et al. CSF glial biomarkers YKL40 and sTREM2 are associated with longitudinal volume and diffusivity changes in cognitively unimpaired individuals. *NeuroImage Clin*. 2019;23:101801. doi:10.1016/j.nicl.2019.101801.
21. Whelan CD, Mattsson N, Nagle MW, Vijayaraghavan S, Hyde C, Janelidze S, et al. Multiplex proteomics identifies novel CSF and plasma biomarkers of early Alzheimer's disease. *Acta Neuropathol Commun*. dezembro de 2019;7(1):169. doi:10.1186/s40478-019-0795-2.