Commentary

Insights into the role of cerebrospinal fluid cytokines in Alzheimer's disease: A commentary on recent findings

Journal of Alzheimer's Disease Reports
Volume 9: 1–3

DOI: 10.1177/25424823251352846
journals.sagepub.com/home/alr

Carlo Manco[1], Matteo Pardini[2,3], Delia Righi[1] and Domenico Plantone[1]

Abstract

We read the study by Bruno et al. (2025), which highlights the interplay between neuroinflammation and cortical activity in Alzheimer's disease (AD). Their findings on IL-4, IL-7, IL-8, and IL-12 levels and their association with EEG alterations complement our recent research on IL-6, GDF-15, and neuronal damage. We discuss the implications of IL-8 in blood-brain barrier permeability and neurodegeneration, the role of *APOE4* in epilepsy-related phenotypes, and the need for better patient stratification. Future studies should explore these inflammatory pathways to clarify the relationship between neurodegeneration and interictal epileptiform discharges in AD.

Keywords

Alzheimer's disease, epilepsy, interleukins, neuroinflammation

Received: 7 April 2025; accepted: 19 May 2025

We read with great interest the recent article by Bruno et al. (2025) entitled "Cerebrospinal fluid cytokine levels affect electroencephalographic activity in Alzheimer's disease".[1] The study investigates the complex interplay between neuroinflammation and cortical activity in Alzheimer's disease (AD) and presents compelling findings. Initially, the authors documented that higher cerebrospinal fluid (CSF) levels of IL-4 were associated with faster EEG background activity, whereas elevated concentrations of IL-7, IL-8, and IL-12 were associated with interictal epileptiform discharges (IEDs). An intriguing aspect is that epileptic activity is linked to the activation of microglia and astrocytes, creating a vicious cycle that leads to the secretion of pro-inflammatory cytokines, ultimately amplifying the neurodegenerative process characteristic of AD.[2]

In our recent study,[3] we documented a significant correlation between CSF IL-6 levels and markers of neuronal damage, such as neurofilament light chain. Additionally, we observed a notable association between CSF GDF-15 levels and cognitive impairment, as measured by the Mini-Mental State Examination, mediated through $A\beta_{1-42}$ levels. We believe that these findings, although not directly related, are complementary to those of Bruno et al. (2025), as they describe a different facet of the same pathogenic loop involving neuroinflammation, synaptic dysfunction, and neurodegeneration. In particular, they further support the idea that the inflammatory response, especially IL-6 production within the central nervous system, is closely linked to neurodegenerative processes.

The data regarding IL-8 are also highly significant. The role of this cytokine in AD pathogenesis is supported by evidence that the IL-8 gene −251T > A polymorphism, which is associated with increased gene transcription, has been repeatedly linked to an increased susceptibility to AD.[4] The findings of Bruno et al. (2025) can be explained by existing literature, which shows that the release of IL-8 from glial cells in vivo can activate CXCR1 and CXCR2 receptors on cholinergic septal neurons, acutely modulating their excitability and reducing calcium currents.[5] IL-8 plays an important role in the recruitment of neutrophils, activating peripheral endothelial cells and leading to the upregulation of

[1]Department of Medicine, Surgery and Neuroscience, University of Siena, Siena, Italy
[2]Department of Neuroscience (DINOGMI), University of Genoa, Genoa, Italy
[3]IRCCS Ospedale Policlinico San Martino, Genoa, Italy

Corresponding author:
Carlo Manco, Department of Medicine, Surgery and Neuroscience, University of Siena, Siena 53100, Italy.
Email: carlooo95.cm@gmail.com

adhesion molecules that facilitate transmigration to the CNS. It has already been demonstrated an association between higher levels of IL-4, IL-8, and blood-brain barrier permeability, with high serum levels of IL-8 in AD patients with white matter hyperintensities.[6–8]

Remarkably, the evidence of the modification of neuronal excitability by pro-inflammatory cytokines is also observed in other diseases, such as in Cytokine Release Syndrome (CRS), which is characterized by the presence of seizures and encephalopathy, along with a systemic inflammatory response triggered by various factors. CRS is often presented concomitantly with immune cell effector-associated neurotoxicity syndrome, a known adverse effect of Chimeric Antigen Receptor T-cell (CAR-T) therapy.[9]

It is also important to note that numerous studies have been published on neuroinflammation in AD, often yielding conflicting results. In this context, meta-analyses have shown that, despite the volume of scientific literature, significant alterations in levels of cytokines are not consistently observed.[10,11] These inconsistencies, accompanied by high heterogeneity across studies, are likely influenced by factors such as insufficient quality control measures and small sample sizes. Moreover, neuroinflammation should be interpreted as a spectrum of the complex inflammatory responses involving the CNS with a continuous crosstalk between central and peripheral immune system.[12] From this perspective, the exclusive investigation of cytokine alterations alone seems quite limited.[13]

From a methodological standpoint, in the study by Bruno et al. (2025) reports an association between levels of IL-7, IL-8, and IL-12 and IEDs.[1] However, the absence of a direct comparative analysis prevents a clear understanding of the differences in cytokine levels between patient groups with and without IEDs. Moreover, the optimal cutoff level of predictive cytokines to discriminate between these two groups has not been defined. The authors stated that analytes concentration below the detection threshold were considered as 0 pg/ml, and cytokines with more than 5% of values below the limit of detection (LOD) were excluded from statistical analysis. We argue that this approach includes values that should be interpreted with caution, as they are not unequivocal. Specifically, filtering data based on the instrument's limit of detection (LOD) rather than on the limits of quantification (lower LOQ and upper LOQ) leads to the inclusion of values that fall outside the "working range" defined by the kit manufacturer. With this comment, we highlight the need for more rigorous quality control procedures in the field of neuroinflammation, which is already characterized by significant methodological and biological heterogeneity.

Another important aspect to better understand the category of patients with EIDs and neurodegeneration could be considering the influence of the *APOE4* allele. This allele is known to alter EEG patterns;[14,15] and *APOE4* has been associated with a seizure phenotype and sex differences compared to *APOE2* and *APOE3* in mice.[16] The influence of *APOE4* is also demonstrated in neuroinflammation where *APOE4* negatively influences plasma IL-7 levels.[17,18] The *APOE* status would therefore be an important piece of information to know in the work of Bruno et al. (2025).

In conclusion, neuroinflammation could represent an important link between neurodegeneration and EIDs in AD. However, a broader understanding of EIDs in this context will require future studies with more detailed patient clustering, including risk factors that may influence neuroinflammation and neuronal excitability.

ORCID iD

Carlo Manco https://orcid.org/0000-0003-4572-2616

Author contributions

Carlo Manco: Data curation; Resources; Supervision; Validation; Visualization; Writing – original draft; Writing – review & editing.
Matteo Pardini: Conceptualization; Data curation; Writing – original draft; Writing – review & editing.
Delia Righi: Conceptualization; Data curation; Visualization; Writing – original draft; Writing – review & editing.
Domenico Plantone: Conceptualization; Data curation; Methodology; Project administration; Supervision; Validation; Visualization; Writing – original draft; Writing – review & editing.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

Declaration of conflicting interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

References

1. Bruno M, Bonomi CG, Castelli A, et al. Cerebrospinal fluid cytokine levels affect electroencephalographic activity in Alzheimer's disease. *J Alzheimers Dis Rep* 2025; 9: 25424823241306772.
2. Vossel KA, Tartaglia MC, Nygaard HB, et al. Epileptic activity in Alzheimer's disease: causes and clinical relevance. *Lancet Neurol* 2017; 16: 311–322.
3. Plantone D, Pardini M, Manco C, et al. CSF IL-6, GDF-15, GFAP and NfL levels in early Alzheimer disease: a pilot study. *Ther Adv Neurol Disord* 2025; 18: 17562864251314773.
4. Righi D, Manco C, Pardini M, et al. Investigating interleukin-8 in Alzheimer's disease: a comprehensive review. *J Alzheimers Dis* 2025; 103: 38–55.
5. Puma C, Danik M, Quirion R, et al. The chemokine interleukin-8 acutely reduces Ca(2+) currents in identified cholinergic septal neurons expressing CXCR1 and CXCR2 receptor mRNAs. *J Neurochem* 2001; 78: 960–971.
6. Bruno M, Bonomi CG, Ricci F, et al. Blood-brain barrier permeability is associated with different neuroinflammatory profiles in Alzheimer's disease. *Eur J Neurol* 2024; 31: e16095.

7. je EC, Janelidze S, van Westen D, et al. Associations between CSF markers of inflammation, white matter lesions, and cognitive decline in individuals without dementia. *Neurology* 2023; 100: E1812–E1824.
8. Zhu Y, Chai YL, Hilal S, et al. Serum IL-8 is a marker of white-matter hyperintensities in patients with Alzheimer's disease. *Alzheimers Dement (Amst)* 2017; 7: 41–47.
9. Satyanarayan S, Spiegel J, Hovsepian D, et al. Continuous EEG monitoring detects nonconvulsive seizure and Ictal-Interictal Continuum abnormalities in moderate to severe ICANS following systemic CAR-T therapy. *Neurohospitalist* 2023; 13: 53–60.
10. Swardfager W, Lanctt K, Rothenburg L, et al. A meta-analysis of cytokines in Alzheimer's disease. *Biol Psychiatry* 2010; 68: 930–941.
11. Chen X, Hu Y, Cao Z, et al. Cerebrospinal fluid inflammatory cytokine aberrations in Alzheimer's disease, Parkinson's disease and amyotrophic lateral sclerosis: a systematic review and meta-analysis. *Front Immunol* 2018; 9: 2122.
12. Bettcher BM, Tansey MG, Dorothée G, et al. Peripheral and central immune system crosstalk in Alzheimer disease — a research prospectus. *Nat Rev Neurol* 2021; 17: 689–701.
13. Leng F and Edison P. Neuroinflammation and microglial activation in Alzheimer disease: where do we go from here? *Nat Rev Neurol* 2020; 17: 157–172.
14. Kim NN, Tan C, Ma E, et al. Abnormal temporal slowing on EEG findings in preclinical Alzheimer's disease patients with the ApoE4 allele: a pilot study. *Cureus* 2023; 15: e47852.
15. Ponomareva NV, Korovaitseva GI and Rogaev EI. EEG Alterations in non-demented individuals related to apolipoprotein E genotype and to risk of Alzheimer disease. *Neurobiol Aging* 2008; 29: 819–827.
16. Hunter JM, Cirrito JR, Restivo JL, et al. Emergence of a seizure phenotype in aged apolipoprotein epsilon 4 targeted replacement mice. *Brain Res* 2012; 1467: 120–132.
17. Zhang YJ, Cheng Y, Tang HL, et al. APOE E4–associated downregulation of the IL-7/IL-7R pathway in effector memory T cells: implications for Alzheimer's disease. *Alzheimers Dement* 2024; 20: 6441–6455.
18. Bonacina F, Coe D, Wang G, et al. Myeloid apolipoprotein E controls dendritic cell antigen presentation and T cell activation. *Nat Commun* 2018; 9: 1–15.