

CSF Biomarkers and APOE4 in AD : Analysis and Review

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Alzheimer disease (AD) is the most prevalent type of dementia, accounting for at least two-thirds of cases in individuals aged 65 and older. It is a neurodegenerative condition with insidious onset and progressive impairment of behavioral and cognitive functions. I use the open dataset '[Plasma lipidomics in Alzheimer's Disease](#)' to analyse the implications of CSF biomarkers and genotype on AD, and integrate the results with insights from relevant studies to provide biological context, to highlight the significance of developing targeted therapies in neurodegeneration research.

Key tools --

Statistical tests (T and Z tests, ANOVA, Tukey)

Data visualization (boxplots, heatmaps)

Python libraries (pandas, seaborn, scipy, statsmodels)

Major Findings -

Amyloid- β and tau significantly differ with AD severity

Significant effects of APOE4 carrier status on A β pathology and cognitive decline

Objectives

1. Characterise CSF Biomarker levels across diagnostic groups :

Alzheimer's Disease is defined by an extensive loss of neurons and synaptic dysfunction caused by deposition of extracellular amyloid- β plaques and intracellular neurofibrillary tangles of hyperphosphorylated tau protein in several cortical regions of the brain. Disease progression is marked by distinct changes in CSF biomarker levels. I aim to quantify these changes in A β , tau and tau phosphorylation among AD, mild cognitive impairment and control groups. Detecting these changes will be helpful to implement therapeutic interventions before plaques, tangles and irreversible cognitive impairment become evident.

2. Assess APOE4 carrier effects on Biomarker levels as an AD risk factor:

Among the increasing number of genetic risk factors identified, the apolipoprotein E (*APOE*) gene remains the strongest and most prevalent, impacting more than half of all AD cases. The primary physiological function of apoE is to mediate lipid transport in the brain and periphery, however, additional functions of apoE in diverse biological functions have been recognized. The E4 allele has been associated with many pathological processes possibly linked to cognitive impairment, such as amyloid- β (A β) and tau pathologies. However, the exact mechanism underlying ApoE4 impact on AD progression is unclear. Assessing biomarker levels in APOE4 homozygotes explains the mechanisms underlying APOE4 neurotoxicity and pathogenic effects.

Amyloid-B and Tau levels across diagnostic groups

Amyloid- β :

Significant difference in concentration across all three groups, showing an inverse relationship with disease severity. The amyloid hypothesis proposes that decrease in CSF amyloid is due to an imbalance in its production and clearance causing increased accumulation of A β as plaques in the CNS (Kwasi G. Mawuenyega *et al.*

2010). In normal subjects, A β is excised from APP by β - and γ -secretase and released outside the cell, where it is rapidly degraded or removed. However, in aged subjects or under pathological conditions, the metabolic ability to degrade A β is decreased, and A β peptides may be accumulated disrupting nerve signalling pathways. This dataset shows that **AB below (466.6–550.4)pg/mL in the CSF is a marker of AD and below (761.6–1462.0)pg/mL warrants monitoring for MCI risk.**

Total and Phosphorylated Tau :

Total tau is significantly higher in CSF in AD compared to control and MCI. However, detecting risk of cognitive impairment in the preclinical stage requires further testing for factors like amyloid B, APOE4 carrier status and PET. CSF Tau levels increase with an increase in disease severity, but this data shows no significant changes in phosphorylated tau. A β fibril formation induces tau hyperphosphorylation (Busciglio J, et al. 1995) which ultimately causes microtubules stabilised by tau to disassemble, free tau molecules to aggregate into paired helical fragments, and tau leakage into CSF increasing total tau levels. Amyloid- β and hyperphosphorylated tau aggregates mutually interact to cause downstream AD neurodegeneration (Pascoal T, et al. 2017).

CSF Tau levels above (494.3–607.9)pg/mL is indicative of AD. Overlap of CI between cognitively normal and mildly cognitive impaired groups shows that total tau cannot reliably distinguish mci from normal aging and require supplemental biomarkers. CSF p-Tau levels are higher in AD patients when compared with healthy controls (Kandimalla RJ, et al. 2013), as it is the main component of paired helical fragments. The 95% CI for p-tau is (76.5–99.1)pg/mL for

AD patients, much higher than that of the control but with significant overlap with the mci group.

Potential reasons for failure to differentiate P-tau levels are low power due to small sample size, high variability and overlap in values. The 95% CI for p-tau is (76.5–99.1)pg/mL for AD patients, much higher than that of the control but with significant overlap with the mci group.

ApoE4 effect on CSF biomarker levels and cognitive decline

This dataset confirms that **ApoE4 carriers are at a higher risk of developing AD**. I explore the effects of the ApoE4 allele on amyloid- β and tau pathologies, along with other mechanisms, that lead to cognitive decline and confer its role in AD pathology.

Amyloid- β :

APOE4 carriers show significantly lower A β levels in both AD and MCI patients. ApoE regulates A β metabolism along with its primary function of cholesterol transport. Astrocytic ApoE4 during the seeding stage of amyloid development enhanced amyloid aggregation and neuritic dystrophy (Liu CC, et al. 2017). High concentrations of apoE form co-aggregates, where apoE4 increases and stabilises A β oligomerisation more than apoE3, harmfully accelerating A β aggregation in AD (Kanekiyo T, et al. 2014, Hashimoto T, et al. 2012). ApoE4 is either more likely to promote A β fibrillogenesis or less effective in preventing A β aggregation, or both (Cerf E, et al. 2011, Naiki H, et al. 1997). ApoE4 antagonises LRP1 (LDL receptor -related protein) for cellular A β uptake, contributing to aggregation rather than soluble A β clearance (Tachibana M, et al. 2019).

Tau :

ApoE4 does not show significant effect on total and phosphorylated tau levels, apart from in mildly cognitive impaired individuals. However, there is an amyloid-independent association between ApoE4 and elevated tau-PET in medial temporal regions (Neitzel J, et al. 2020). In A β -dependent tau pathology, following the deposition of A β plaques in the brain, deposition of insoluble tau aggregates starts years later. The major effect of APOE4 on tau accumulation is mediated by A β , surpassing the impact of A β -independent ApoE4 on tau levels (Cicognola C, et al. 2025).

ApoE4 displays lower transport affinity and binding capacity for lipids (Hatters DM, et al. 2006), which could reduce cholesterol transport from astrocytes to neurons. As a result, ApoE4 mediated cholesterol dysregulation affects synaptic function and contributes to cognitive decline. Lysosomal cholesterol degradation processes are also impaired in ApoE4 astrocytes, damaging

structural and metabolic supports of neurons (Jeong W, et al. 2019). Thus the ApoE4 allele seems to be the most influential factor for AD, especially in late-onset AD due to its effects on A β and tau pathology, cholesterol metabolism and neuroinflammatory effects leading to cognitive decline exacerbated by age.

ApoE4 as a therapeutic target in AD:

Modulations of ApoE gene and apoE properties are promising targets for therapeutic interventions to AD. Targeted elimination of apoE4 may be an encouraging strategy to reduce its toxic effects. An anti-apoE4 monoclonal antibody (9D11) likely prevented the apoE4-driven cognitive impairment and brain tau hyperphosphorylation in apoE4-TR mice [Michaelson DM, et al. 2014]. Inhibition of the apoE-A β interaction by a synthetic peptide (A β 12-28P: homologous to the apoE binding site on the full-length A β) resulted in reduced A β accumulation, and memory deficits in amyloid mouse models (Liu S, et al. 2014). In addition to pharmacological approaches using compounds and peptides, ApoE gene delivery is a promising strategy to regulate brain apoE levels. Adeno-associated virus mediated ApoE gene delivery reduced AB aggregation in apoE4-TR mice (Hu J, 2015). Increasing lipidation of apoE4 can reverse apoE4-induced cognitive and neuronal deficits (Price AR, et al. 2013).

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