BIOMARKERS OF SYNAPTIC IMPAIRMENT AND NEUROINFLAMMATION IN THE ALZHEIMER'S DISEASE CONTINUUM

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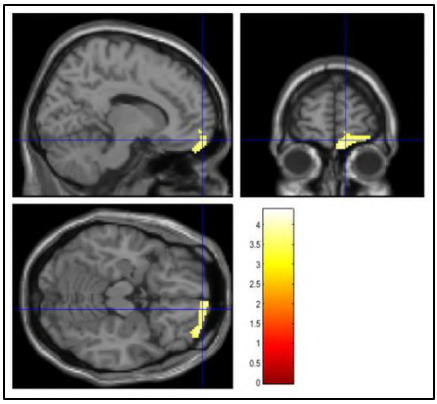
Background

Neuroinflammation and synaptic impairment are recognized as pathogenic mechanisms of Alzheimer's disease (AD).[1] Biomarkers such as glial fibrillary acidic protein (GFAP), a marker of astrocytic activation, and soluble TREM2 (sTREM2), a marker of microglial activation, are promising for monitoring disease progression.[2] Synaptic dysfunction, an early hallmark of AD, is reflected in biomarkers such as synaptosome-associated protein 25 (SNAP-25), a presynaptic protein linked to neurotransmitter release.[3] This study aimed to explore the role of neuroinflammatory and therefore the use of synaptic biomarkers across the AD continuum.

Methods

The cohort included 69 cognitively impaired patients within the AD continuum, evaluated at the Memory Clinic of the University of Torino. All patients underwent a comprehensive neuropsychological assessment, including Mini-Mental State Examination (MMSE). Based on Clinical Dementia Rating (CDR) scores, participants were classified as having mild cognitive impairment (MCI; CDR=0.5, n=34) or dementia (D; CDR≥1, n=35). According to the available CSF Aβ42, Aβ40, p-Tau181, and t-Tau the cohort was stratified using the AT(N) framework into A+/T– (n=13) and A+/T+ (n=56) groups. CSF concentrations of GFAP, sTREM2, SNAP-25, and neurofilament light chain (NfL) were measured using the Simoa (Quanterix) platform. Statistical analyses included Spearman's correlation, linear regression, and generalized linear models with adjustment for demographics, APOE status, and core AD biomarkers. In subset of patients with at least one longitudinal MMSE data (n=39), a linear mixed-effects model was applied to evaluate the predictive value of biomarkers on cognitive decline.

Figure 1. Voxel-wise association between FDG-PET SUVR and GFAP.



Statistical parametric map revealed a significant association between GFAP levels and regional brain metabolism measured with FDG-PET. A cluster located in the right medial and orbitofrontal prefrontal cortex was observed. These findings indicate that higher GFAP values are associated with FDG-PET uptake in prefrontal cortical regions.

Results

CSF levels of NfL and GFAP were significantly higher in D compared to MCI (p=0.029 and p=0.030, respectively), while sTREM2 and SNAP-25 did not differ between groups. Moreover, GFAP correlated positively with p-Tau181 (rho=0.41, p=0.001). sTREM2 correlated positively with with p-Tau181 (rho=0.32, p=0.012) and negatively with the Aβ42/40 ratio (rho=-0.38, p=0.003). SNAP-25 showed no significant correlation with core AD biomarkers.
No baseline associations were found between neuroinflammatory or synaptic biomarkers and cognitive scores. However, elevated GFAP levels predicted a longitudinal decline of MMSE score over a period of 20 months (β=-3.14, p=0.047), independent of age, education and APOE status.

Discussion

This study shows the relevance of neuroinflammatory and synaptic biomarkers across the AD continuum. The most informative marker resulted to be GFAP, discriminating among cognitive stages and predicting longitudinal decline. These findings support the role of astrocytic activation in AD, and its potential application in clinical follow-up to track disease progression.

References
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