Plasma protein associations with hippocampal atrophy across the cognitive spectrum from normal aging to Alzheimer's disease

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Abstract

Background: We recently reported lower plasma levels of interleukin 13 (IL13), tissue inhibitor of metalloproteinases 1 (TIMP1), and angiopoietin 2 (ANG2) in apolipoprotein E4 (*APOE4*) positive subjects relative to *APOE4* negative subjects at risk for familial Alzheimer's disease (FAD). Here, we investigated the correlation of these plasma protein levels with hippocampal atrophy in the ADNI sample.

Methods: We analyzed the imaging and plasma protein biomarker data from the Alzheimer's Disease Neuroimaging Initiative (ADNI) study. Our sample included 475 subjects – 58 normal controls, 310 MCI and 107 AD subjects of whom 244 were *APOE4* carriers and 231 *APOE4* non-carriers. Baseline EDTA plasma samples were collected and analyzed with a 190 analyte multiplex immunoassay panel based on the Luminex xMAP platform. Hippocampal segmentations were generated from 1.5T 3D T1-weighted brain MRI scans with a novel automated segmentation technique based on the AdaBoost machine learning method. Hippocampal thickness was analyzed with the radial distance technique. We applied linear regression models to study the associations between IL13, TIMP1, and ANG2 plasma protein levels and hippocampal radial distance. Our linear regression models were adjusted for age and gender. We ran analyses in the pooled sample and then separately in *APOE4* carriers and non-carriers. For multiple comparisons correction, we used permutations with threshold $p<0.01$.

Results: High levels of IL13, a well-established inflammatory protein, showed a significant negative association with right hippocampal radial distance in the pooled sample ($\beta=-0.31$, $p_{corrected}=0.039$). High levels of TIMP1, a protein that promotes cell proliferation and has an anti-apoptotic function, showed a significant negative association with hippocampal radial distance in the pooled sample on the left ($\beta=-0.42$, $p_{corrected}=0.027$). ANG2, a regulator of neuronal progenitor differentiation and migration, showed a significant positive association with hippocampal radial distance on the right in *APOE4* carriers ($\beta=0.53$, $p_{corrected}=0.018$), but a significant negative association on the left in *APOE4* non-carriers ($\beta=-0.2$, $p_{corrected}=0.026$).

Conclusion: Hippocampal atrophy in the ADNI cohort was associated with plasma levels of several proteins whose plasma levels were previously reported to differ between *APOE4* carriers and non-carriers in a presymptomatic FAD cohort.

Figure 1. Significance and ß coefficient maps showing the association of IL13, TIMP1 and ANG2 serum concentrations with hippocampal radial distance in the pooled sample (N=475), *APOE4* carriers (N=244) and *APOE4* non-carriers (N=231).