Low serum levels of ApoE associate with hippocampal atrophy in the ADNI cohort

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Abstract

Background: The search for Alzheimer's Disease (AD) protein biomarker signatures is ongoing. Taking into account the long latent stage of AD and the ease of access to peripheral blood samples, it is an important endeavor to find serum or plasma proteins that may be useful for presymptomatic diagnosis.

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 (NC), 310 MCI and 107 AD subjects of whom 244 were apolipoprotein E4 gene (*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 created 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 hippocampal radial distance and several promising plasma protein AD biomarkers – apolipoprotein E (ApoE), apolipoprotein J (ApoJ), brain derived neurotrophic factor (BDNF), heat shock protein 40 (HSP40), interleukin 6 (IL6) and tumor-necrosis factor α (TNFα). Our linear regression models were adjusted for age and gender in the pooled sample. Considering a possible modulation by *APOE4* genotype, we also ran separate analyses in the *APOE4* carrier and non-carrier groups. For multiple comparisons correction, we used permutations with a threshold of $p<0.01$.

Results: Plasma ApoE levels showed significant positive associations with hippocampal radial distance in the CA1 and subicular regions bilaterally in the pooled sample (left $\beta=0.28$, $p_{corrected}=0.001$; right $\beta=0.23$, $p_{corrected}=0.046$; **Figure 1**, *top row*). Regionally significant positive associations were present bilaterally in *APOE4* carriers (left $\beta=0.14$; right $\beta=0.27$; **Figure 1**, *middle row*). The association pattern in *APOE4* non-carriers was different from that seen in *APOE4* carriers, especially on the right where it took a negative direction (left $\beta=0.19$; right $\beta=-0.18$; **Figure 1**, *bottom row*). ApoJ, BDNF, TNFα and IL6, failed to show significant association with hippocampal radial distance (maps not shown).

Conclusion:

Decreased plasma levels of ApoE, a protein with amyloid β binding properties that plays a role in amyloid β clearance and a known modulator of zinc- and copper-induced amyloid β aggregation, showed significant association with hippocampal atrophy in the pre-dementia cognitive spectrum. This suggests a potential role for ApoE plasma levels in pre-dementia diagnostic ascertainment.

Figure 1. Significance and ß coefficient maps showing the association between plasma ApoE levels and hippocampal radial distance in the pooled sample (N=475, *top row*), *APOE4* carriers (N=244, *middle row*) and *APOE4* non-carriers (N=231, *bottom row*)