Interactions between apolipoprotein E, sex, and amyloid-beta on cerebrospinal fluid p-tau levels in the European Prevention of Alzheimer’s Dementia Longitudinal Cohort Study (EPAD LCS)

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Abstract

Background: Alzheimer’s Disease, the leading cause of dementia, is over-represented in females. The apolipoprotein E (APOE) ε4 allele is the strongest genetic risk factor for late-onset AD and is associated with aberrant cerebrospinal fluid levels (CSF) of total tau (t-tau), phosphorylated tau (p-tau), and amyloid-β (Aβ). There is some evidence that sex may mediate the relationship between APOE status and CSF tau, however, evidence is mixed.

Method: We aimed to examine the association between sex, APOE ε4 status, CSF Aβ on t-tau and p-tau in 1776 mid-to-late life individuals without a diagnosis of dementia in the European Prevention of Alzheimer’s Dementia (EPAD) longitudinal cohort study.

Result: We found a significant interaction between APOE status, sex, and CSF Aβ on CSF p-tau levels. Specifically, the association between CSF Aβ and CSF p-tau was stronger in male ε4 carriers relative to female ε4 carriers. Further, in females with high Aβ levels (reflecting less cortical deposition), ε4 carriers had significantly elevated p-tau levels relative to non-carriers. However, there were no significant differences in p-tau between male ε4 carriers and non-carriers with high Aβ.

Conclusion: An interaction between sex and cerebrospinal fluid Aβ may mediate the relationship between APOE status and CSF p-tau. These data suggest tau accumulation may be independent of Aβ in females, but not males. Future work would benefit from replication in separate cohorts, longitudinal examination, and the consideration of the role of sex hormones on CSF markers.