Analysis of Cerebral Small Vessel Changes in an APOE4 Knock-In AD Mouse Model

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Introduction:

Alzheimer's disease (AD) is a complex neurodegenerative disorder and the leading cause of dementia worldwide. Recently approved monoclonal antibody therapy has shown increased instances of amyloid-related imaging abnormalities (ARIA) in patients with the APOE4 allele compared to those with the APOE3 allele. Although it is well established that AD adversely affects cerebral vasculature, the differential pathology between alleles is not fully understood. This study aims to explore and quantify the changes of cerebral small vessels in a human APOE4 vs. APOE3 knock-in AD mouse model.

Methods:

Brains were collected from APOE3: APP-SAA and APOE4: APP-SAA mouse cohorts at 8 months. Sectioning and staining were completed with immunofluorescence imaging of beta-amyloid (6E10), blood vessel (CD31), and microglia (Iba1) biomarkers. Vessel density, diameter, signal intensity, and vessel-plaque colocalization were analyzed using NIH Fiji software, and t-tests were performed to compare averages between cohorts.

Results:

Two-tail t tests revealed a vessel density difference of -0.4956±0.4590% ($t(8)=1.080;p=0.3118$) and a CD31 intensity difference of -269881±169413au ($t(8)=1.593;p=0.1498$) showing no statistical significance. Further testing showed a vessel diameter difference of -0.4043±0.02431 um ($t(700)=16.63;p<0.0001$). Additionally, testing showed a plaque-vessel colocalization difference of 16.34±6.307% ($t(51)=2.591;p=0.0124$). The qualitative assessment showed higher levels of microglial activation, a marker of neuroinflammation, in APOE4: APP-SAA brain samples.

Discussion:

The APOE4 allele is associated with adverse changes in cerebral small vessels in a controlled APOE3 vs. APOE4 APP-SAA model. The observed pathology of increased neuroinflammation, decreased vessel diameter, and heightened amyloid-beta localization to cerebral small vessels may elucidate the mechanisms by which monoclonal antibody therapy targeting plaque removal results in increased pathological side effects related to vessel damage. These findings warrant further studies on vascular changes responding to AD progression across ages and investigations into how this novel model may respond to monoclonal antibody therapy experiments.