

Intravenous anti-A β immunotherapy acutely increases cerebral amyloid angiopathy and vascular damages in APOE4 mice



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TAKE HOME: Cerebral amyloid angiopathy (CAA) increases acutely in 3D6-treated APOE4 mice. These increases correlate with APOE4-preferential plaque clearance, border associated macrophage expression, vascular changes, and microhemorrhage incidence.

Introduction: Anti-A β immunotherapies for Alzheimer's Disease (AD) are associated with high rates of amyloid-related imaging abnormalities (ARIA), an adverse side effect with markedly higher rates in APOE4 carriers. The mechanism of ARIA, particularly at acute timepoints, and the role of APOE genotype remain unknown.

Methods: Over 100 4-month-old 5xFAD/GFP/APOE3 and 5xFAD/GFP/APOE4 mice were treated intravenously (via tail vein injection) with a single dose of anti-A β antibody 3D6 or IgG1 control (5 mg/kg). Mice were euthanized at 1-, 3-, and 10-days post-treatment and analyzed for plaque numbers, CAA incidence, border associated macrophage, and microhemorrhages using immunofluorescence, ELISA, vessel isolation, Prussian Blue staining, and T1*-weighted MRI. An additional cohort of mice receiving 4 injections of 3D6 was added for some analyses.

MODEL

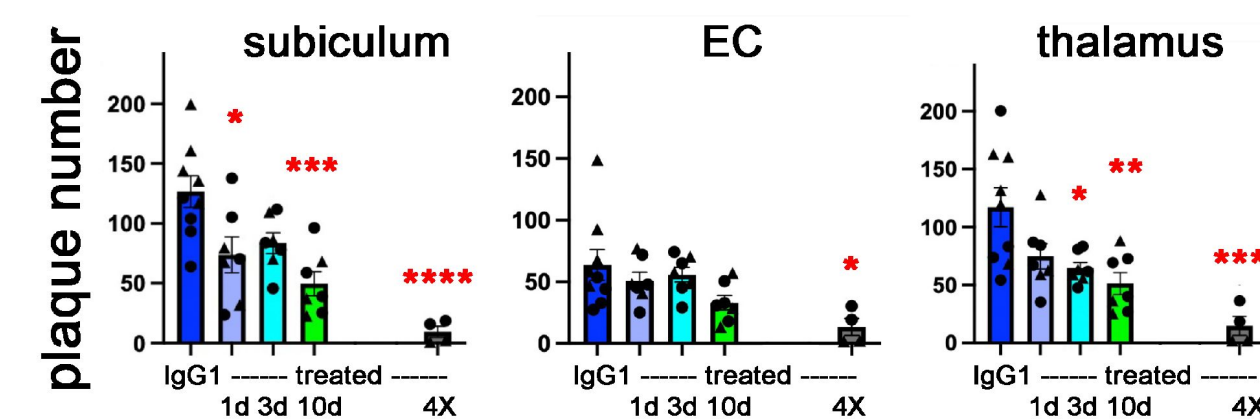
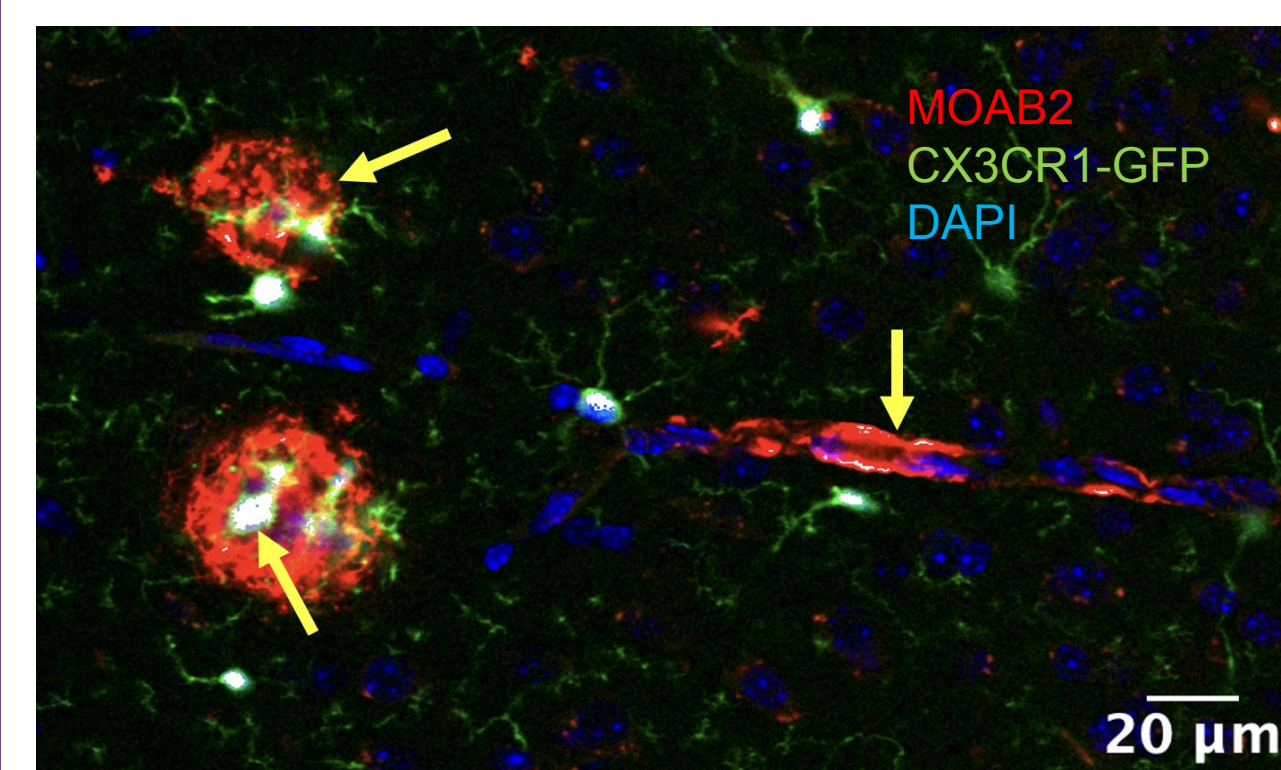


Figure 1: Representative image of plaques and CAA in our mouse model (top panel). Plaques were cleared from APOE4 mice by IV 3D6 as early as one day post-treatment across brain regions (bottom). Further clearance occurred in mice treated with with four doses over two weeks (4X). Little clearance occurred in APOE3 mice (not shown).

RESULTS 1

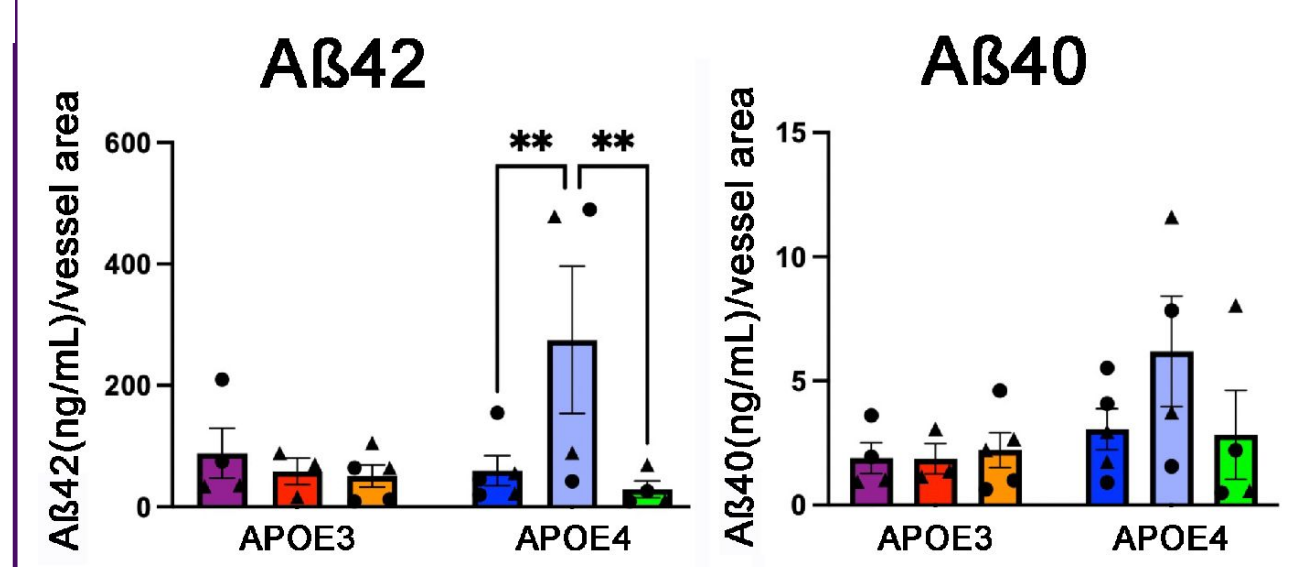
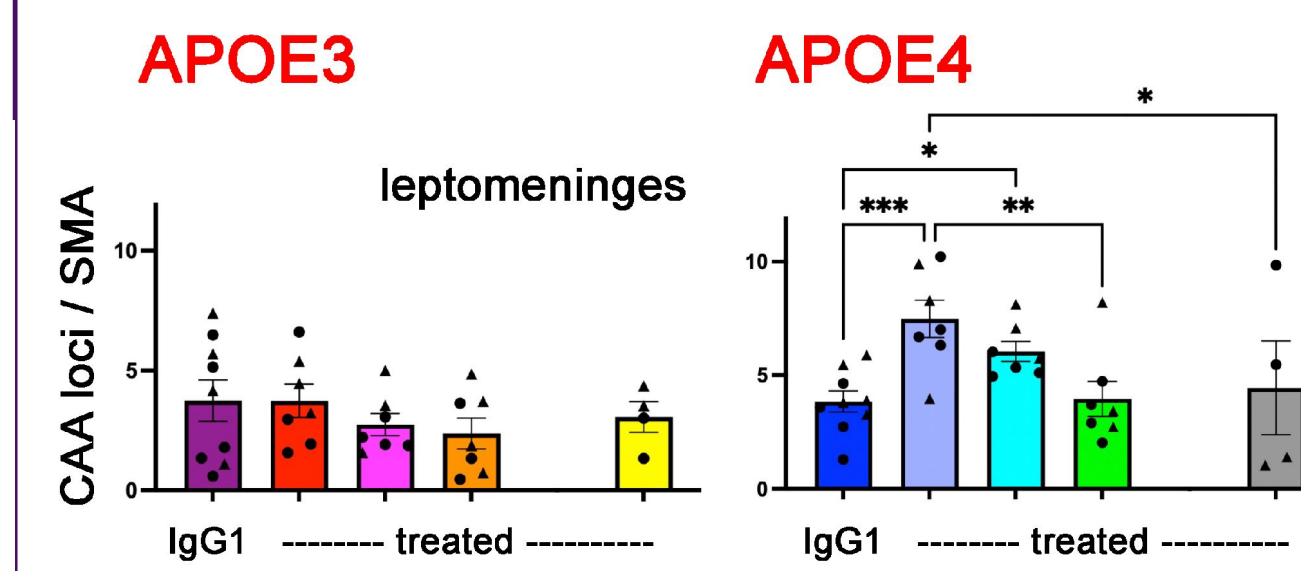
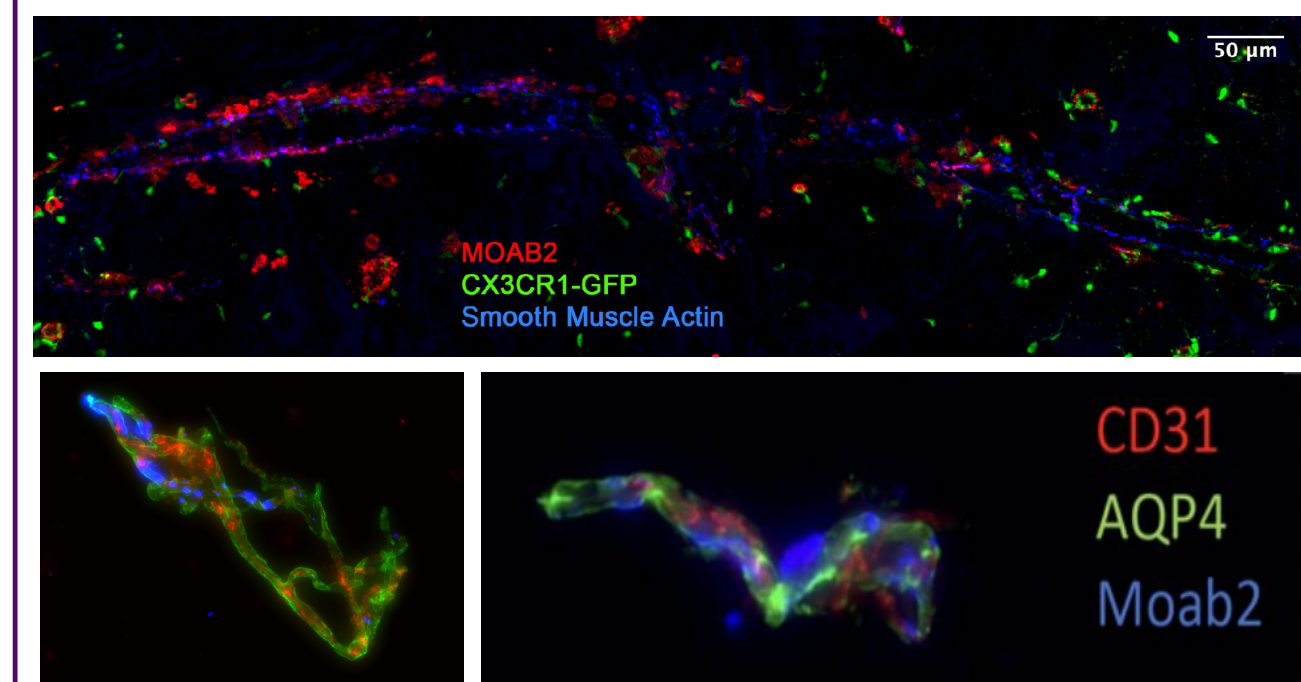


Figure 2: 3D6 increased CAA incidence both in fixed tissue (top) and in isolated cerebral blood vessels (bottom) within one day.

RESULTS 2

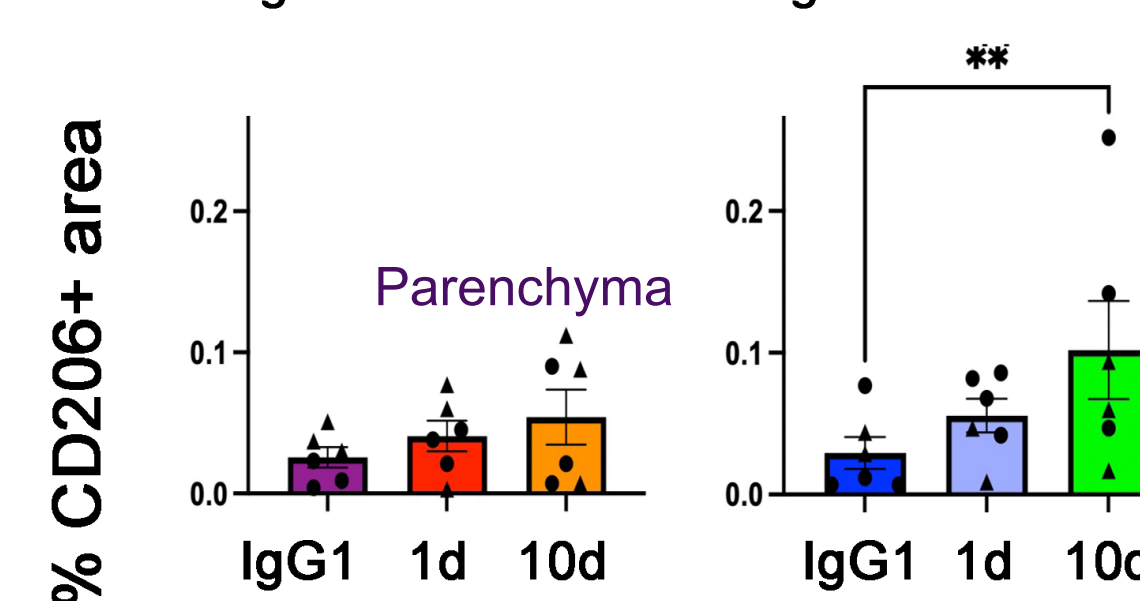
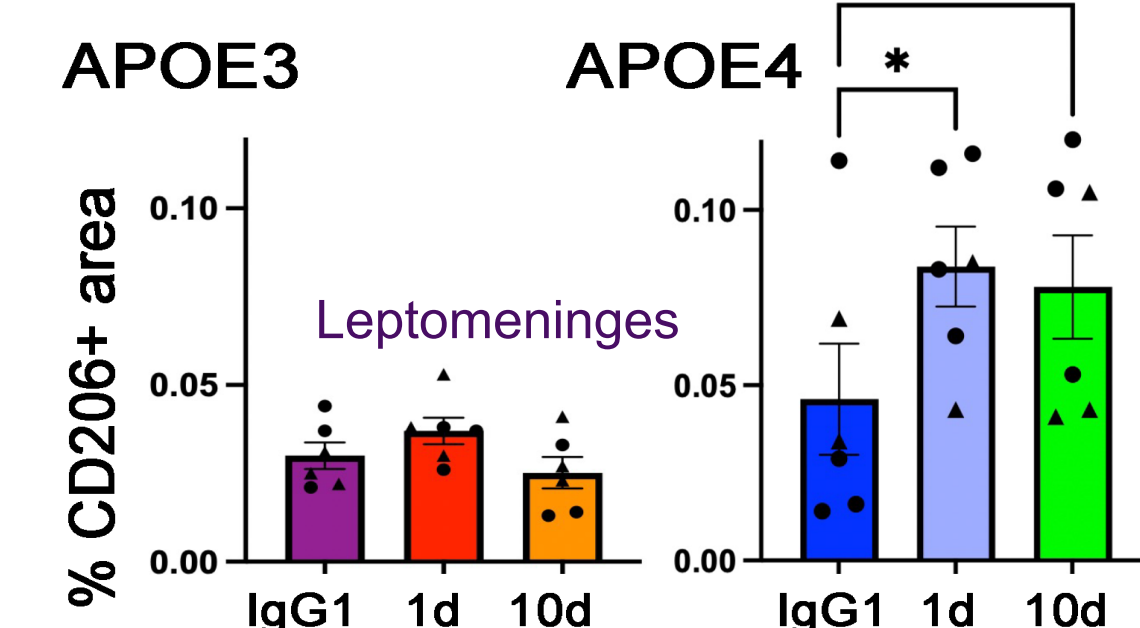
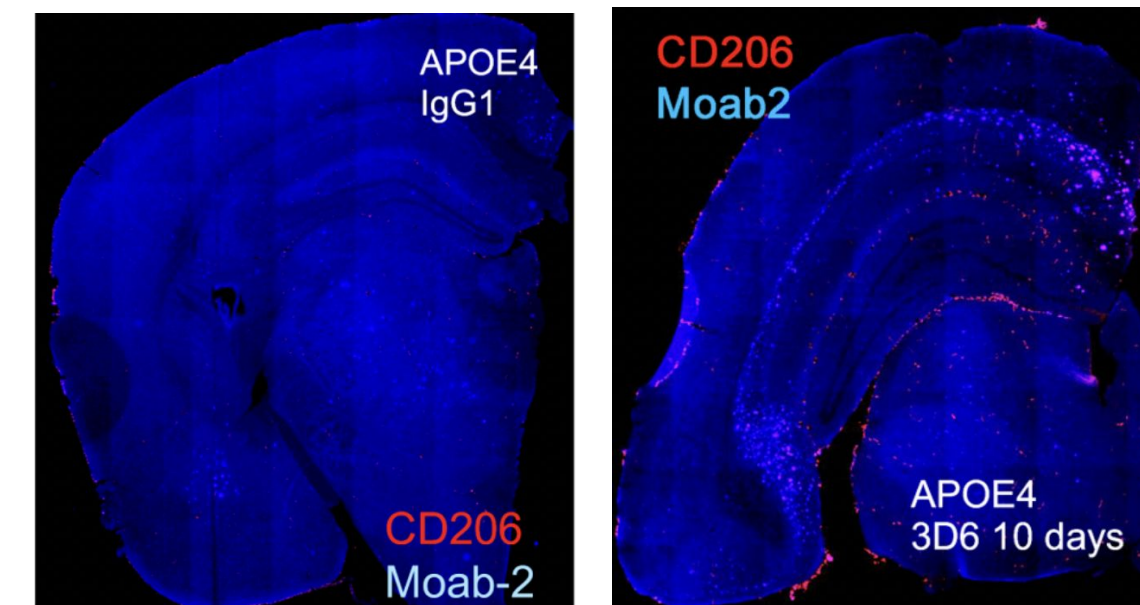


Figure 3: Border Associated Macrophage (CD206+) increased in leptomeninges (top) and parenchyma (bottom) of treated APOE4 mice.

RESULTS 3

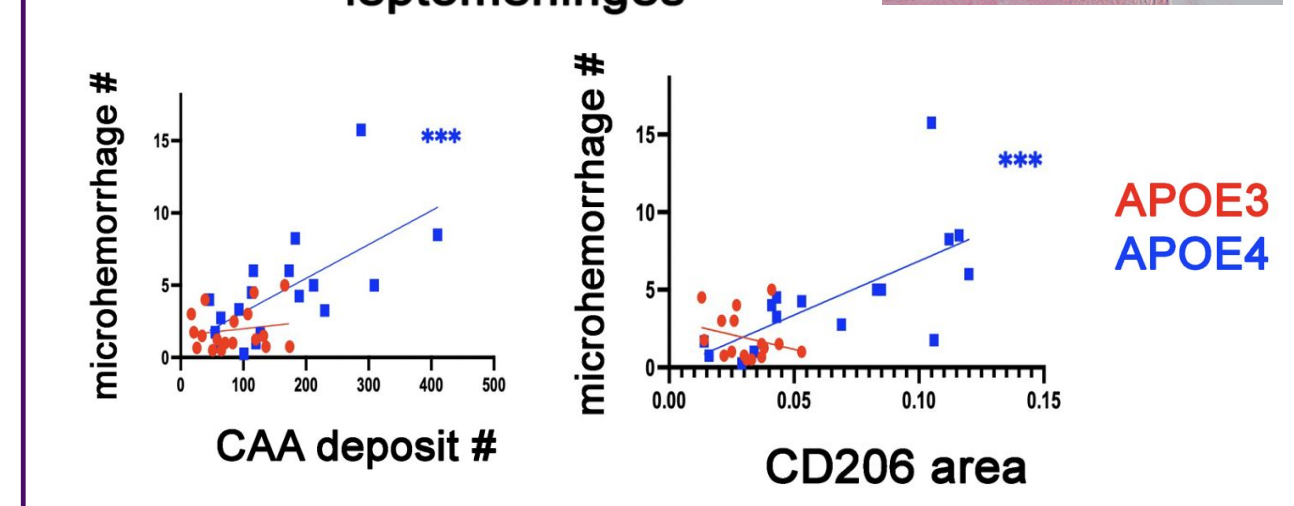
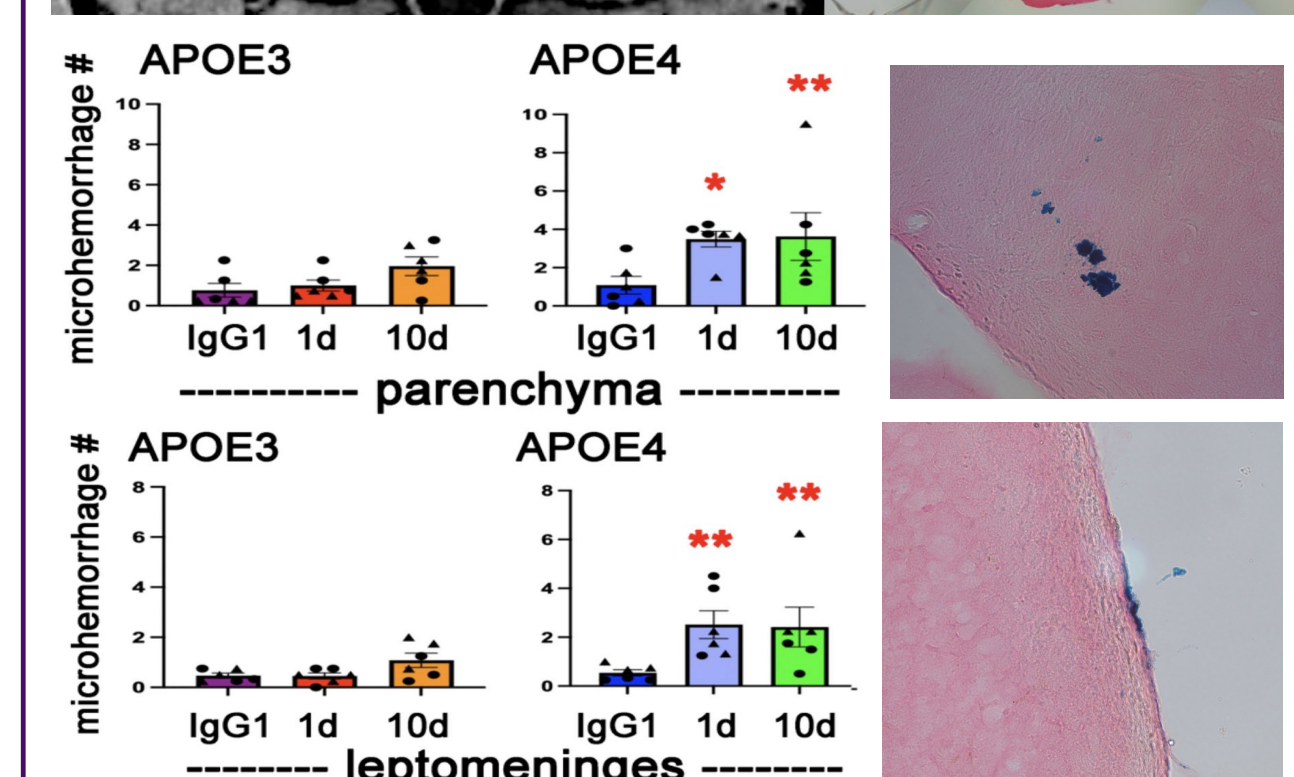
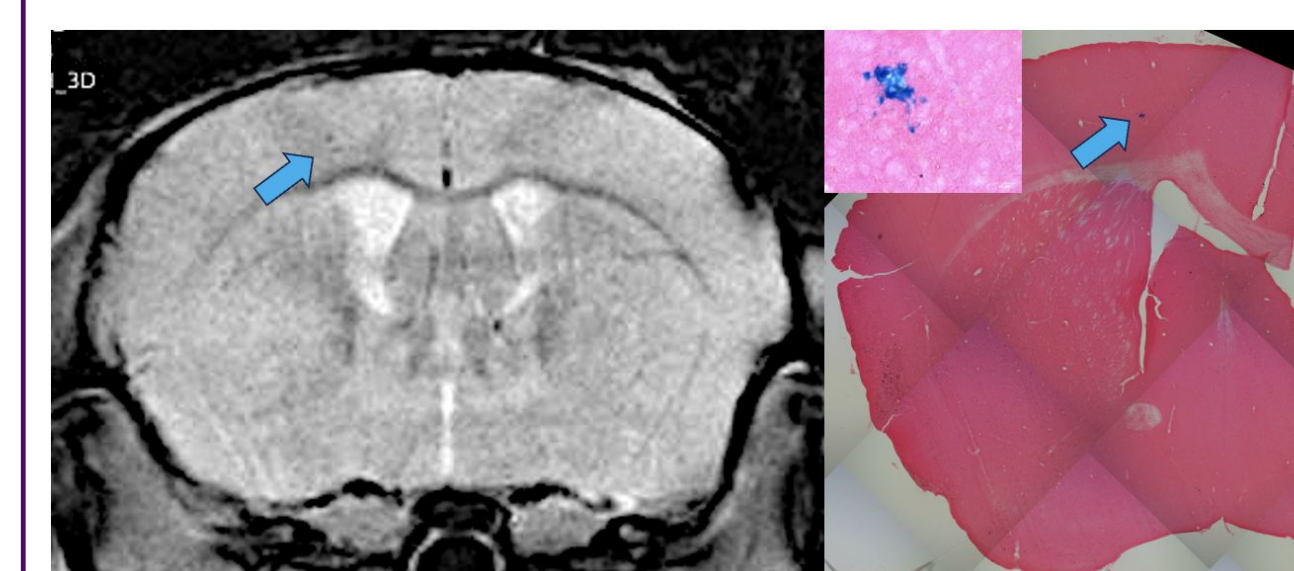


Figure 4: APOE4 mice had increased microhemorrhages as measured on both histology and MRI; microhemorrhages correlated significantly with CAA deposits and BAM area.

CONCLUSIONS

- A single dose of 3D6 preferentially reduced amyloid in APOE4 mice within one to ten days.
- CAA increased within one day in 3D6-treated APOE4 mice across cohorts and analysis modalities.
- BAMs increased in 3D6-treated APOE4 mice.
- Microhemorrhages correlated significantly with both CAA and BAMs increases.
- There is an induction of ARIA-related pathogenesis within days after a single anti-A β antibody IV injection, specifically in APOE4 mice.