RETINAL AMYLOID BETA LOAD IS ASSOCIATED WITH CEREBRAL AMYLOID ANGIOPATHY IN PATIENTS WITH DEMENTIA

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## PURPOSE

Alzheimer disease (AD) is a neurodegenerative disorder characterized by excessive amyloid beta (Aβ) deposition in the brain. Definitive diagnosis of AD is only possible by autopsy. Currently, surrogate tests such as positron emission tomography (PET) is used to measure cerebral Aβ burden, but this is expensive and involves radiation exposure. The retina is a neuro-sensory extension of the central nervous system that can be readily visualized, making it a viable candidate for an accessible AD biomarker complementary to brain imaging. Aβ in the retina has been reported in several AD-transgenic murine models. The purpose of this study is to assess the retinal Aβ load in AD and normal donors in order to test the hypothesis that retinal Aβ load is related to cerebral amyloid angiopathy (CAA).

METHODS

Autopsy materials from donors with AD and non-AD dementia (retina, brain) and age-matched healthy donors (retina) were processed. Brain samples were evaluated for neuritic and diffuse senile plaques (CERAD score), Aβ protein (Thal phase), neurofibrillary tangles (Braak stage) and CAA. Retinal samples were processed as free floating punches (3 mm) and paraffin embedded cross sections (6 um) using mouse monoclonal Aβ antibodies (6F/3D) and Cy3 secondary antibodies. The punches were taken from the fovea, peri-fovea, and 3 peripheral cardinal direction (superior, temporal, and inferior regions). Each punch was imaged on a Zeiss 510 confocal microscope with Zen 2009. Retinal Aβ load was measured quantitatively in Cy3-stained images by pixel counting. The artifacts and cells were masked out in Image J. In the remaining regions, the number of pixels with intensity level above a fixed threshold was computed. To account for varying sizes of the artefactual regions, the pixel count was normalized by the area of the non-masked search region.

RESULTS

We collected retinal and brain samples from 16 donors with AD (n=11) and non-AD dementia (n=5). Additionally, retina tissue from 10 control (healthy) donors were also examined. Both intra-and extracellular retinal Aβ were assessed. Among the brains with dementia, 9 had negative (n=4) to mild (n=5) CAA, and were categorized as CAA1. The remaining 7 brains with dementia showed moderate (n=3) to severe (n=4) CAA, and were categorized as CAA2. The group-mean Aβ load for the control, CAA1, and CAA2 groups were compared using Kruskal-Wallis multiple comparison test. The CAA2 group showed significantly greater retinal Aβ load in all retinal regions as compared with the control (P<.001) and the CAA1 (P=.004) groups. Between the CAA1 and the control groups, significant retinal Aβ load difference was observed only in the superior and temporal regions (P=.013).
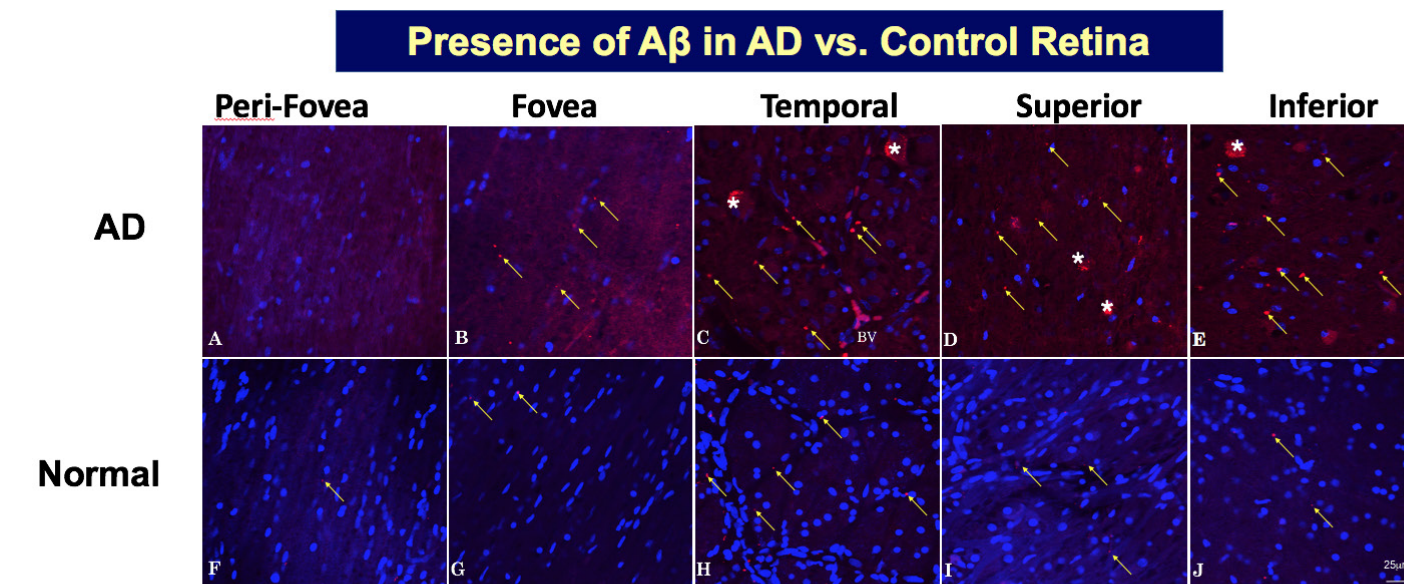
Representative images of retinal punches from AD (A-E) and Control (F-J) eyes immunoreacted for Aβ (red) and counterstained with DAPI for nuclei (blue). Note strong Aβ immunoreactivity in the peripheral regions (temporal, superior and inferior) of the AD eye that includes intracellular (asterisks) and extracellular deposits (arrows), and retinal vasculature (BV). Control eyes have low levels of extracellular deposits (arrows).

CONCLUSION

High retinal Aβ load was associated with moderate to high cerebral amyloid angiopathy in patients with dementia. This study is the first to characterize intra- and extracellular Ab in the retinal tissue of Alzheimer's patients. The results of this study lend credence to the potential of retinal Aβ imaging as a minimally invasive AD screening method.

COMMENTS

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