Retinal Imaging Biomarkers for Early Diagnosis of Alzheimer’s Disease

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Provocative Hypothesis: Alzheimer’s Disease *may be an eye disease* as well as a brain disease.
AD patients exhibit visual function defects and retinal changes

- Patients with early AD experience abnormalities in visual acuity, contrast sensitivity, color perception, visual field, and motion perception.
- Many of the retinal findings associated with AD have been detected early in disease course and mirror neurodegenerative changes in the brain.
Retinal Biomarkers Would be a “Game-Changer” for Alzheimer’s Disease (AD)

- AD is the only one of America’s leading causes of death that has no preventive or curative treatment.
- Drug development and patient care are hampered by lack of accurate, early diagnostic tests.
- Glimmer of hope brought by recent phase 1B study.

March 20, 2015

BIOGEN IDEC PRESENTS POSITIVE INTERIM RESULTS FROM PHASE 1B STUDY AT 2015 AD/PD CONFERENCE

ADUCANUMAB (BIIB037) REDUCED BRAIN AMYLOID PLAQUE LEVELS AND SLOWED COGNITIVE DECLINE IN PATIENTS WITH PRODROMAL OR MILD ALZHEIMER’S DISEASE IN PHASE 1B STUDY.
Accurate retinal biomarkers for early AD would be a “game-changing” discovery

• Current diagnostic modalities for AD are limited by cost (MRI, PET), invasiveness (CSF biomarkers), suboptimal specificity and sensitivity (genetic markers, serum amyloid), length of evaluation and access to specialists (neuropsychological evaluation).

• We expect that retinal imaging biomarkers will be as sensitive and specific as serum/CSF amyloid or genetic tests as well as more sensitive, more specific, and less costly than MRI/PET imaging.

Retinal imaging is noninvasive, fast, and high resolution (100X of MRI).
Considering that the retina is a developmental outgrowth of the brain, the retina may be vulnerable to the same inflammatory injury that causes neurodegenerative disease in the brain.

Why might AD be associated with changes in the retina?

Monocytic cells in AMD retina

Monocytic cells in AD brain
Converging Evidence: NFL thinning in AD and MCI patients, compared to cognitively intact peers

30 AD, 24 MCI, 24 Controls

AD and MCI groups had thinner Inferior NFL vs. Control

AD group also had thinner superior NFL vs. Control

Kesler et al. Clin Neurol Neurosurg 2011
New SD-OCT: NFL is thinner in AD patients, compared to cognitively intact peers


N=21 in each group; excluded glaucoma & AMD
Peripheral Retinal Drusen as a Potential Surrogate Marker for Alzheimer’s Dementia: A Pilot Ultra-Wide Angle Imaging Study

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PURPOSE: The development of Alzheimer’s dementia (AD) and age-related macular degeneration (AMD) share similar histopathology, vascular risk factors and genetic predisposition and both are characterized by extracellular deposit formation. In this study we examined the prevalence and spatial distribution of macular and peripheral retinal pathologies in patients with AD.

METHODS: Colour and autofluorescent (AF) images were taken by the Optos P200C AF ultra-wide angle laser scanning ophthalmoscope (200°) to determine phenotypic variations in 56 AD patients and 46 controls. Images were graded for the prevalence of drusen, pigmentary changes, atrophy or choroidal neovascularisation (CNV) in the macula as well as retinal periphery. The periphery was divided into two zones (zone 4 and 5) to extend the standard AMD grid and pathological distribution was recorded in four sectors within these zones. All subjects had blood taken for genotyping. Comparisons were made using the chi-squared test after adjustment for potential confounders.

RESULTS: There was a positive genetic association between AD and ApoE4 RS429358 (p=0.09). Only one control, but 4 patients were diagnosed to have AMD based on macular pathologies. In the periphery hard drusen were present in 14/55 (25.4%) of AD patients and 2/48 (4.2%) of controls [Chi2=9.0, df=4, p=0.04]. After adjustment for age and history of transient ischemic attack, this association remained strongly significant (p<0.001).

DISCUSSION: Ultra-wide angle imaging revealed a potential association between AD and AMD and a highly significant association between AD and peripheral hard drusen formation. These findings suggest that monitoring for the development and progression of pathological changes in the macula and most importantly in the periphery might become a valuable tool in detecting and monitoring the progression of AD. Further work is required to develop the understanding of this association which may lead to peripheral drusen acting as a surrogate marker for plaque development in the central nervous system.

![Peripheral grading result](image1.png)

Figure 1. Images were graded for typical AMD categories such as hard drusen, soft drusen, geographic atrophy (GA) and choroidal neovascularisation (CNV). The only significant difference in peripheral retinal grading between controls and AD patients was detected in hard drusen. There was no CNV detected at the far periphery.

![Image grading grid](image2.png)

Figure 2. Image grading grid (A) for grading ultra-wide angle images. (B-H) show typical imaging of AD patients. (B) far peripheral hard drusen deposits, (C-D) images taken through cataract are still gradable, (E-F) typical lid and eye-lash artifacts.

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**Question:** With careful neurocognitive characterization and age-matching, exclusion of confounders (glaucoma, ERM artifacts etc), precise layer segmentation using novel software, will ocular biomarkers predict early AD?
Pilot Study – Alzheimer’s Association and Duke Institute for Brain Science

- **Design:** Case-control study with 1-year follow-up
  - 18 patients with MCI/prodromal AD
  - 18 patients with mild-to-moderate AD
  - 18 control subjects, cognitively normal and age-matched.

*To our knowledge, will be first study to have all these:*
- 3 robustly characterized neurocognitively and age-matched cognitive groups
- Careful exclusion for AMD and glaucoma (esp. normal tension), as well as image artifacts (ERM etc)
- 1 year follow up of cognition and retinal biomarkers
To our knowledge, will be first study to have all these (cont.)

- Spectral domain OCT of macula and optic nerve, wide field fundus color and autofluorescence photo, and stereo disc photography
To our knowledge, will be first study to have all these (cont.)
- extremely accurate semi-automatic segmentation of retinal layer thickness (DOCTRAP software)

Sina Farsiu
Director, Vision & Image Processing Lab
Excluding ERM artifacts
Preliminary Analysis Oct. 2014

• Our preliminary analysis 10/14 showed a statistically significant difference between neurocognitive status of 14 control subjects and 10 mild-moderate AD subjects but did not reveal a reduction in NFL/GCL in AD patients.

• Careful exclusion of normal tension glaucoma may account for these preliminary findings.

• However, since this analysis, we identified some promising signals in NFL/GCL and peripheral drusen in the larger population analyzed.
Examples of quadrant-specific NFL thickness abnormalities around the optic nerve

Mild-moderate AD (A, B), MCI (C), and control subjects (D) in our study.

Red: abnormal
Yellow: borderline
Green: normal.

Maps obtained with native SD-OCT RNFL Heidelberg software; similar trends observed with DOCTRAP.
Thickness maps generated by DOCTRAP

NFL Thickness Map

GCCL Thickness Map

Foveal OCT Image
More examples: Mild-moderate AD

Severe thinning of NFL was only found in AD subjects, not MCI or control patients
Loss was typically superior or inferior
More cases: MCI

- Moderate thinning of NFL is common in MCI subjects
- Excluded MCI subjects (2) due to suspicion of NTG, but subjects were not deemed to have glaucoma
- Location of NFL loss is variable
More cases: Control

We identified borderline NFL in 3 control subjects, but all these were deemed to be NTG suspects by glaucoma specialists
Semi-qualitative Drusen Grading

- Grade 0: None
- Grade 1: 1-20
- Grade 2: 21-50
- Grade 3: >50

Grade 0
Grade 3
Semi-qualitative Drusen Grading

- Grade 0: None
- Grade 1: 1-20
- Grade 2: 21-50
- Grade 3: >50

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>MCI</th>
<th>AD</th>
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</thead>
<tbody>
<tr>
<td>Any drusen</td>
<td>35.3 %</td>
<td>38.5 %</td>
<td>62.5 %</td>
</tr>
<tr>
<td>Grade 3 drusen</td>
<td>17.7 %</td>
<td>7.7 %</td>
<td>25 %</td>
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Quantitative Drusen Grading on Color and FAF (DOCTRAP)
Next Steps

• Final Recruitment (age-matching, exclude glaucoma)
• Complete detailed SD-OCT analysis by clock hours; exclude areas of artifact (ERM)
• Quantification of drusen/deposits on wide-field color fundus photo and auto-fluorescence
• Association with age related macular degeneration (AMD)? *We found higher AD prevalence with increasing severity of age-related macular degeneration* (tomorrow’s poster).
• 1 year follow-ups examinations: progression of biomarkers
Conclusions

- Careful neurocognitive characterization, age matching, exclusion of normal tension glaucoma and artifacts (ERM) are critical.
- Although preliminary analysis of control/AD patients was negative, we identified some promising signals in NFL/GCL and peripheral drusen in the larger population analyzed.
- Comparison of retinal images between normal subjects and subjects with different stages of cognitive impairment (prodromal and mild-moderate AD) will allow evaluation of the most promising retinal-based imaging biomarkers for early AD (OCT, color/AFC changes, vascular).
- Our interdisciplinary, collaborative group is well equipped to perform this analysis robustly and to determine if the retina is the window to the brain for early AD.
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