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FROM THE ALZHEIMER'S ASSOCIATION INTERNATIONAL CONFERENCE 2016

SMELL AND EYE TESTS ONE STEP CLOSER FOR DETECTION OF MEMORY DECLINE AND DEMENTIA

- New Alzheimer's biomarker results suggest potential for simpler, lower-cost tests -

TORONTO, July 26, 2016 – The potential of odor identification testing and physical changes in and around the eye to detect cognitive impairment and Alzheimer's disease at an early stage was bolstered by new evidence from four studies presented today at the Alzheimer's Association International Conference (AAIC) 2016.

Two studies evaluated changes in odor identification as an early predictor of cognitive decline, or of the transition to dementia, and compared it to two established biological markers for cognitive decline and dementia - brain amyloid PET imaging and thickness of the brain's cortex in areas important to memory.

Two other studies reported at AAIC 2016 found:
● A strong association between thinning nerve layers in the retina of the eye and poor cognition, suggesting the potential of retinal imaging as part of early Alzheimer's testing.
● The presence of amyloid deposits in the retina of both people with Alzheimer's and canine models of the disease by non-invasive polarization imaging; this strengthens their utility as a marker of Alzheimer's, and a possibility for pre-symptomatic detection.

"It's clear that the science around biological measures in the detection of Alzheimer's continues to gather pace and validation," said Heather Snyder, PhD, director of medical and scientific operations, Alzheimer's Association. "Low cost, non-invasive measures to detect dementia-related changes and evaluate the risk of future decline continue to be refined and tested; this is a positive step forward to earlier detection and intervention."

Today, it is only possible to clinically detect Alzheimer's relatively late in its development, when significant brain damage has already occurred. While brain positron emission tomography (PET) imaging can show the buildup of amyloid plaques in the brain years before symptoms appear, PET scans are expensive. Beta amyloid can also be detected in cerebrospinal fluid (CSF) through a lumbar puncture, and brain PET imaging of abnormal tau protein is rapidly advancing through research.

"Using other biomarkers of Alzheimer's disease to detect the disease at an earlier stage - which have the potential to be lower-cost and non-invasive - could lead to dramatic improvements in early detection and management of the disease," Snyder said.

Predictive Utility of Entorhinal Cortex Thinning and Odor Identification Test for Transition to Dementia and Cognitive Decline in an Urban Community Population
Growing research evidence suggests that decreased ability to correctly identify odors is a predictor of cognitive decline and an early clinical feature of Alzheimer's disease. The 40-item University of Pennsylvania Smell Identification Test (UPSIT), can be used to test ability to identify odors.

Seonjoo Lee, PhD, and colleagues from Columbia University Medical Center, administered UPSIT to 397 people average age 80 from a multiethnic community in North Manhattan, all non-demented at baseline, who also had an MRI scan, and followed them over four years. The goal was to better understand the usefulness of UPSIT in detecting the transition to dementia and cognitive decline, and to compare it with thinning of the entorhinal cortex, the first area of the brain to be affected by Alzheimer's disease.

During follow-up, 50 people (12.6 percent) transitioned to dementia (49 to Alzheimer's disease), and 19.8 percent were classified as cognitive decliners.
- Both lower odor identification scores on UPSIT and, to a lesser degree, entorhinal cortical thickness were significantly associated with the transition to dementia and Alzheimer's disease controlling for age, education, gender, language of UPSIT administration (English or Spanish), functional status and intracranial volume.
- Lower baseline UPSIT scores, but not entorhinal cortex thickness, predicted cognitive decline in study participants.
- Entorhinal cortical thickness was significantly associated with UPSIT among participants who transitioned to dementia.

"Our research showed that odor identification impairment, and to a lesser degree entorhinal cortical thickness, were predictors of the transition to dementia," said Lee. "These findings support odor identification as an early predictor, indirectly suggesting that impairment in odor identification may precede thinning in the entorhinal cortex in the early clinical stage of Alzheimer's disease."

Both Odor Identification and Amyloid Status Predict Memory Decline in Older Adults
William Kreisl, MD, and colleagues from Columbia University Medical Center, sought to assess the utility of odor identification impairment and beta amyloid PET or CSF analysis in predicting memory decline in older adults. They did this by determining both UPSIT scores and amyloid status in 84 participants (58 with amnestic mild cognitive impairment and 26 control subjects, age 68 ± 7 years, 58% female, education 16 ± 3 years) who had either brain amyloid PET or lumbar puncture at baseline, plus at least six months follow-up.

At follow-up, 67 percent of participants showed memory decline. After correcting for age, sex and education, amyloid-positivity determined by PET scan or lumbar puncture predicted decline while UPSIT score did not. However, participants with a UPSIT score less than 35 were more than three times more likely (OR=3.95, p=0.0192) to have memory decline than those with a UPSIT score greater than 35.

"Our research suggests that both UPSIT score and amyloid status predict memory decline," Kreisl said. "Younger age, higher education, and shorter follow-up may explain why UPSIT did not predict decline as strongly in this study as in previous studies," Dr. Kreisl said. "While more research is needed, because the UPSIT is much less expensive and easier to administer than PET imaging or lumbar puncture, odor identification testing may prove to be a useful tool in helping physicians counsel patients who are concerned about their risk of memory loss."

Retinal Nerve Fiber Layer Thinning Associated with Poor Cognitive Function Among a Large Cohort

Fang Ko, MD, and colleagues from the Moorfields Eye Hospital, UCL Institute of Ophthalmology, London, in collaboration with members of the Topcon Advanced Biomedical Imaging Laboratory in Oakland, New Jersey, and the University of Oxford explored associations between cognition and retinal nerve fiber layer (RNFL) thickness using spectral domain optical coherence tomography (SD-OCT).

The retinal nerve fiber layer is formed by the expansion of the fibers of the optic nerve, which transmits visual information from the retina to the brain. Thickness of the RNFL is known to decrease with age. Findings from several small clinical studies suggest that RNFL may be associated with cognitive performance. The researchers used the United Kingdom Biobank study to test this hypothesis in a large community-based population sample.

In this study, 33,068 participants underwent macular SD-OCT, physical examination, cognitive testing and answered a questionnaire. Cognitive measures were prospective memory, pairs matching, numeric and verbal reasoning, and reaction time.

The researchers found a significant association between thinner macular RNFL and poor cognition:
- RNFL was thinner among those with any one abnormal cognitive test.
- For the prospective memory test, mean RNFL thickness was 53.3μm among those who recalled correctly on first attempt versus 52.5μm on second attempt, and 51.9μm for those who did not recall.
- Thinner RNFL was associated with poorer pairs matching, numeric and verbal reasoning, and reaction time on univariate regression.
- Effects appeared additive for each additional cognitive test failed; RNFL was significantly thinner by 1.0μm.

"Our findings show a clear association between thinner macular RNFL and poor cognition in the study population," Ko said. "This demonstrates the potential utility of the eye as a non-invasive measure of neuronal loss which is linked to cognitive performance, and provides a possible new biomarker for studies of neurodegeneration."

"These exciting findings show the value of large-scale studies for identifying new biomarkers, strengthening considerably the evidence for neuronal loss in the eye being an indicator of neuronal loss more generally, and may lead to the discovery of new mechanisms of neurodegeneration," said Praveen Patel, MB, BChir, MA, FRCOphth, MD(Res), of Moorfields Eye Hospital, UCL Institute of Ophthalmology, London, and senior author of this study.

"Many older adults routinely visit their ophthalmologist, so incorporating this technology - once proven - into annual eye care visits could aid in assessing cognitive status and identifying individuals that should have further evaluation by a healthcare professional," Snyder added.

Amyloid as a Biomarker of Alzheimer's Disease in Post-Mortem Retinas in Human and the Canine Model of Alzheimer's Disease

Currently, the presence of amyloid in the brain is measured using PET brain scans that are expensive, not generally covered by insurance, and not always locally available. After death, evidence of beta amyloid in the brain in association with a history of dementia is the gold standard for diagnosis of Alzheimer's disease. As an inexpensive alternative to PET scans, polarized light may detect protein deposits in the retina. This method requires no dyes or invasive testing.

Melanie Campbell, Ph.D., and colleagues from the University of Waterloo, Ontario, Canada, the University of Rochester, University of British Columbia, Massachusetts General Hospital, Vivocore Inc. and Intervivo Solutions, compared amyloid deposits in the neural retina of humans and in a canine model of Alzheimer's to assess their visibility using several different imaging methods, and reported the results at AAIC 2016.

The researchers analyzed diseased eyes from 20 humans and six canines, alongside 22 control human retinas and seven control canine retinas. Atomic force, confocal and polarization microscopes were used. Retinas of five canines were imaged *in vivo* in amyloid fluorescence and clinical optical coherence tomography (OCT) for comparison.

Retinal amyloid deposits were seen using a polarized microscope that did as well as the more invasive fluorescence imaging technique in detecting the amyloid. A fluorescence marker for amyloid crossed the blood retinal barrier *in vivo* in the canine model of AD and identified amyloid deposits that did not appear in the OCT contrast images.

"Polarization imaging is promising for noninvasive imaging of retinal amyloid deposits as a biomarker of Alzheimer's," Campbell said. "The ability to detect amyloid deposits in the retina prior to disease symptoms may be an essential tool for the development of preventative strategies for Alzheimer's and other dementias."

"Cognitive dysfunction syndrome is a naturally occurring condition in canines with similar changes in the brain to those in humans with Alzheimer's, including the accumulation of beta amyloid with increasing age. The amyloid deposits in canine retinas had very similar properties to the deposits imaged in human retinas, such as being located close to nerve cells and exhibiting interaction with polarized light. Studying cognitive dysfunction syndrome in this animal may give improved understanding of Alzheimer's in humans," Campbell added.

About the Alzheimer's Association International Conference (AAIC)
The Alzheimer's Association International Conference (AAIC) is the world's largest gathering of researchers from around the world focused on Alzheimer's and other dementias. As a part of the Alzheimer's Association's research program, AAIC serves as a catalyst for generating new knowledge about dementia and fostering a vital, collegial research community.
AAIC 2016 home page: www.alz.org/aaic/
AAIC 2016 newsroom: www.alz.org/aaic/press.asp

About the Alzheimer's Association
The Alzheimer's Association is the leading voluntary health organization in Alzheimer's care, support and research. Our mission is to eliminate Alzheimer's disease through the advancement of research, to provide and enhance care and support for all affected, and to reduce the risk of dementia through the promotion of brain health. Our vision is a world without Alzheimer's. Visit alz.org or call 800.272.3900.

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- Seonjoo Lee, PhD, et al. Predictive Utility of Entorhinal Cortex Thinning and Odor Identification Test for Transition to Dementia and Cognitive Decline in an Urban Community Population. (Funder: U.S. National Institute on Aging)
- William Kreisl, MD, et al. Both Odor Identification and Amyloid Status Predict Memory Decline in Older Adults. (Funder: U.S. National Institute on Aging)
- Fang Ko, MD, et al. Retinal Nerve Fiber Layer Thinning Associated with Poor Cognitive Function Among a Large Cohort, UK Biobank. (Funder(s): University College of London; International Glaucoma Association)
- Melanie Campbell, PhD, et al. Amyloid As a Biomarker of Alzheimer's Disease in Post-Mortem Retinas in Human and the Dog Model of Alzheimer's Disease. (Funder(s): Canadian Institutes of Health Research; The Natural Sciences and Engineering Research Council of Canada)

Proposal ID: O3-12-02
Tuesday, July 26, 2016, 4:15-5:45 pm. Metro Toronto Convention Center, 107
Topic selection: Biomarkers: Eyes and Noses in the Search for Biomarkers for Dementia

Predictive Utility of Entorhinal Cortex Thinning and Odor Identification Test for Transition to Dementia and Cognitive Decline in an Urban Community Population.

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Background: Neuropathology in the olfactory system occurs in the early stages of Alzheimer's disease (AD). Impairment in odor identification, evaluated with the 40-item University of Pennsylvania Smell Identification Test (UPSIT), predicted dementia transition and cognitive decline in a community-based study. The purpose of this study was to examine the predictive utility of the UPSIT on transition to dementia and cognitive decline as it relates to neurodegeneration in the entorhinal cortex.

Methods: 397 Participants (age 79.85±5.21 years, 67 percent female, education 10.82±4.89 years) from a multiethnic community cohort in North Manhattan, non-demented at baseline, who had both MRI and UPSIT, were followed over four years. Cortical thickness in the entorhinal cortex was computed using the Freesurfer (v5.1). Composite cognitive domain scores were derived for memory, language, and visual-spatial ability. Cognitive decline was defined as decrease of 1 standard deviation (SD) over 4 years or 0.5 SD over 2 years on composite scores in at least one cognitive domain.

Results: During follow-up, 12.6 percent of participants developed dementia and 19.8 percent were classified as cognitive decliners. 63 percent of decliners and 5 percent of non-decliners developed dementia (Odds Ratio OR 10.27; p<0.0001). UPSIT (Hazard Ratio HR 1.74 per 1SD; p<0.001) and entorhinal cortical thickness (HR 1.50 per 1SD; p=0.012) predicted the transition to dementia controlling for age, education, gender, language of UPSIT administration (English or Spanish), functional status and intra-cranial volume. UPSIT predicted cognitive decline (OR 1.49 per 1SD; p=0.005), but entorhinal cortical thickness was at trend-level in this prediction (OR 1.08 per 1SD; p= 0.065) controlling for covariates. Entorhinal cortical thinning was significantly associated with UPSIT among participants who transitioned to dementia (r=0.48, p<0.0001), while no association was found in cognitive decliners (r=0.09, p=0.896).

Conclusions: Odor identification impairment, and to a lesser degree entorhinal cortical thickness, were predictors of the transition to dementia. Their high correlation among individuals who transited to dementia supports the view that odor identification deficits are related to neurodegenerative changes in the entorhinal cortex during the progression of AD. The findings indirectly suggest that impairment in odor identification may precede thinning in the entorhinal cortex in the early clinical stage of AD.

Proposal ID: O3-12-01
Tuesday, July 26, 2016, 4:15-5:45 pm. Metro Toronto Convention Center, 107
Topic selection: Biomarkers: Eyes and Noses in the Search for Biomarkers for Dementia

Both Odor Identification and Amyloid Status Predict Memory Decline in Older Adults

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Background: Odor identification can be inexpensively tested using the 40-item University of Pennsylvania Smell Identification Test (UPSIT), and odor identification deficits have been shown to predict cognitive decline in both community-based and memory clinic-based cohorts (1,2). We compared the predictive utility of odor identification to that of amyloid status determined by 11C-Pittsburgh Compound B (PIB) PET or CSF analysis.

Methods: UPSIT score and amyloid status were determined for 81 subjects (55 with amnestic MCI and 26 controls, age 71 ± 7 years, 56 percent female, education 16 ± 3 years) who had either PIB imaging or lumbar puncture at baseline, plus at least 6 months follow-up. Amyloid-positivity was defined as either CSF Aβ42< 192 pg/mL or global PIB uptake > 1.5. Decline was defined as decrease of 1 SD over 4 years or 0.5 SD over 2 years on composite z-score from Logical Memory 1, Visual Reproduction, and Free and Cued Selective Reminding Tests. Data from MCI patients and controls were combined to increase statistical power. Logistic regression and Receiver Operating Characteristic Curve analysis were conducted to test predictability of amyloid-positivity and UPSIT score on memory decline.

Results: At follow-up, 67 percent of participants showed memory decline. After correcting for age, gender, and education, amyloid-positivity predicted decline (OR = 7.31; 95 percent CI = 1.330, 40.234; p = 0.0222) while UPSIT score, as a continuous variable, did not (OR = 1.040; 95 percent CI = 0.944, 1.145; p = 0.429). However, participants with UPSIT score < 35 were more likely to have memory decline than those with UPSIT score $\geq$ 35 (OR = 4.03; 95 percent CI = 1.026, 15.84; p = 0.0459).

Conclusions: Both UPSIT score and amyloid status predict memory decline. While these results suggest that amyloid status may be a stronger predictor, younger age, higher education, and shorter follow-up in this study may explain why UPSIT did not predict decline as strongly as in earlier studies. A larger study with longer follow-up may better determine the ability of odor identification to predict memory decline in participants with high cognitive reserve.

References: 1. Devanand, et al. Neurology. 2015; 84:182-9.
2. Devanand, et al. Biol Psychiatry. 2008; 64: 871–9.

Proposal ID: O3-12-03
Tuesday, July 26, 2016, 4:15-5:45 pm. Metro Toronto Convention Center, 107
Topic selection: Biomarkers: Eyes and Noses in the Search for Biomarkers for Dementia

Retinal Nerve Fiber Layer Thinning Associated with Poor Cognitive Function Among a Large Cohort, UK Biobank

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Background: UK Biobank is a multi-site community-based study of UK residents aged 40–69 years registered with the National Health Service (2007-2010). Our aim is to determine associations between cognition and retinal nerve fiber layer (RNFL) thickness on spectral domain optical coherence tomography (SD-OCT).

Methods: Participants underwent macular SD-OCT, physical examination, cognitive testing, and questionnaire. We randomly selected one eye from 33,068 people with high-quality OCT images. We excluded people with visual acuity <20/25, refraction <-6 or >6 D, IOP <6 or >21 mmHg, any history of ocular or neurologic disease, or diabetes. Cognitive measures were prospective memory, pairs matching, numeric and verbal reasoning, and reaction time. Cognition was graded poor if recall was not achieved on first prospective memory test, or if worse than 95 percent of participants for all other tests. Multivariable regression modeling was used to adjust for age, sex, race, Townsend deprivation index, height, refraction, and IOP, and identify relationships between RNFL thickness and cognitive function. All macular subfields were analyzed, but outer nasal RNFL thickness is reported here, as it was the most sensitive to changes in cognitive function. Statistical significance was defined as P<0.05.

Results: Mean RNFL was significantly thinner among those with any one abnormal cognitive test. For the prospective memory test, mean RNFL thickness was 53.3μm (95 percent CI 53.4-53.6μm) among those who recalled correctly on first attempt, versus 52.5μm (95 percent CI 52.3-52.7μm) on second attempt, and 51.9μm (95 percent CI 51.4-52.4μm) for those who did not recall. Significantly thinner RNFL was linked to poorer pairs matching, numeric and verbal reasoning, and reaction time on univariate regression (each P<0.001). Effects appeared additive for each additional cognitive test failed; RNFL was significantly thinner by 1.0μm (95 percent CI 0.8-1.2μm). Even after controlling for age, all associations remained significant at P<0.001. In the final multivariable regression model, thinner RNFL was associated with worse performance on pairs matching (0.13μm [95 percent CI 0.02-0.23μm]/incorrect match); numeric and verbal reasoning (0.14μm [95 percent CI 0.09-0.19μm] for every 2 points lower in score); and slower reaction time (0.14μm [95 percent CI 0.05-0.22μm] per 100 msec slower).

Conclusions: There is significant association between thinner macular RNFL and poor cognition.

Proposal ID: O3-12-05
Tuesday, July 26, 2016, 4:15-5:45 pm. Metro Toronto Convention Center, 107
Topic selection: Biomarkers: Eyes and Noses in the Search for Biomarkers for Dementia

Amyloid As a Biomarker of Alzheimer's Disease in Post-Mortem Retinas in Human and the Dog Model of Alzheimer's Disease

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Background: As a biomarker of Alzheimer's disease (AD), we compare amyloid deposits in the neural retina in human and in the dog model of AD and their visibility in differing imaging modalities.

Methods: Diseased eyes were from humans with a diagnosis of AD and age matched control eyes had no associated dementia or glaucoma diagnoses. Diseased and normal dogs were positive and negative for cognitive dysfunction syndrome respectively, diagnosed via cognitive impairment testing. Retinas were flat mounted and stained with fluorescent amyloid markers. Atomic force, confocal and polarization microscopies were used to image amyloid positive areas and negative areas of positive retinas and control retinas. 20 AD and 22 control human retinas and 6 positive and 7 negative dog retinas were analyzed. Retinas of 5 dogs, injected IV, were imaged in vivo in amyloid fluorescence and clinical optical coherence tomography (OCT).

Results: Atomic force and confocal microscopies localized amyloid deposits to the anterior neural retinal layers. Amyloid fluorescence occurred with similar high sensitivities and lower specificities in human and dog retinas. Retinal amyloid deposits showed contrast in polarized light, similar to that of pure amyloid beta deposits. The sensitivity and specificity of polarized light in identifying amyloid were similar to the more invasive fluorescence imaging. A fluorescence marker for amyloid crossed the blood retinal barrier in vivo in the dog model of AD and imaged presumed amyloid deposits which showed no contrast in OCT images.

Conclusions: The presence of amyloid deposits with similar properties in the neural layers of human and dog retinas, in those positive for disease, strengthens their utility as a biomarker of AD. The specificity found is close to that of PET amyloid scans, suggesting that amyloid deposits are present in the retina prior to disease symptoms. The similarities between the deposits in the two species support the use of the dog model of AD. The resemblance of polarized light interaction between the retinal amyloid deposits and pure amyloid beta is consistent with the retinal deposits containing a high concentration of amyloid beta. Polarization imaging is promising for non-invasive imaging of retinal amyloid deposits as a biomarker of AD.

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