Hallmark Alzheimer's disease changes found in retinas of humans and imaged in live animals

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The nerve cell-damaging plaque that builds up in the brain with Alzheimer's disease also builds up in the retinas of the eyes - and it shows up there earlier, leading to the prospect that noninvasive optical imaging of the eyes could lead to earlier diagnosis, intervention and monitoring of the disease, according to new research.

Scientists discovered characteristic amyloid plaques in retinas from deceased Alzheimer's disease patients and used a noninvasive optical imaging technique to detect retinal plaques in live laboratory mice genetically modified to model the human disease. The combined results suggest the possibility that noninvasive retinal imaging may be helpful in early diagnosis of the disease.

The research was conducted by a team of scientists at Cedars-Sinai Medical Center in collaboration with colleagues from the Weizmann Institute of Science in Israel and the University of Southern California. Results were published online June 13 in the journal *NeuroImage*, and related findings will be presented July 13 at the Alzheimer's Association International Conference on Alzheimer's Disease.

Alzheimer's disease is a devastating condition that is becoming more prevalent worldwide as the baby-boom generation advances into its senior years, but there is no conclusive, noninvasive way to diagnose it. Previous studies have suggested that changes in the brain may begin

years or even decades before symptoms occur - emphasizing the need for earlier, reliable detection for early therapeutic intervention to achieve effective remedy. The new study suggests the possibility of monitoring Alzheimer's disease through a simple retinal imaging approach.

Abnormal deposits in the brain called beta-amyloid plaques, which damage cells and interrupt cell-to-cell communications, are recognized as a hallmark sign of the disease. However, because existing noninvasive brain-imaging technologies cannot provide sufficient detail about these changes, the most definitive diagnosis of Alzheimer's disease comes after an autopsy.

The research team considered the retina a better target for noninvasive imaging of Alzheimer's disease because it is readily accessible and, unlike other components of the eye, it is part of the central nervous system, having a direct connection and thus many similarities with the brain. Previous studies have documented non-specific visual disturbances, eye disorders and certain types of retinal abnormalities occurring with Alzheimer's disease and other neurodegenerative conditions, but this is the first to identify human retinal plaque deposits that could provide a specific diagnostic marker of Alzheimer's disease.

Among the new findings:

1. In lab tests, plaques in the retinas of mice genetically modified to model Alzheimer's disease could be detected at a very early, pre-symptomatic stage - before the plaque appeared in the brain.

2. A high-resolution, noninvasive optical imaging approach was developed to monitor individual beta-amyloid plaques in the retinas of live mice. The system is based on a harmless specific

marker and the adaptation of an existing optical system used to examine rodent eyes.

3. The research team used a fluorescent compound called curcumin to label and detect retinal plaques. This is believed to be the first use of curcumin as an imaging agent to detect Alzheimer's disease-related plaques in the retinas of live animals. Curcumin, a natural component of the spice turmeric, binds to beta-amyloid plaques and makes them visible when viewed microscopically. In the Cedars-Sinai research, curcumin injected into the bloodstream of live mice crossed the blood-retinal barrier and specifically bound to the retinal plaques, allowing them to be viewed in high resolution with a noninvasive procedure.

4. Observations from multiple genetically engineered mouse models of Alzheimer's disease demonstrated a correlation between retinal plaques and brain plaques as disease progressed.

5. In the laboratory mice, a unique immune system-based therapy that reduces the amount of plaques in the brain also reduced plaque load in the retina to the same extent, suggesting that the retina could faithfully represent the brain in assessing response to therapy.

6. Beta-amyloid plaques were identified in retinal samples from human patients who had died from Alzheimer's disease, and their features correlated with the diagnosed stage of the disease. Importantly, plaques were clearly detected not only in patients who definitely had the disease, but also in the retinas of some people who were suspected of having early-stage Alzheimer's disease based on clinical diagnosis and microscopic examination of brain tissue after death. Together, the results offer the first evidence for the existence of Alzheimer's-specific plaques in the

retina of human patients and the ability to detect individual plaques in live mouse models, creating a strong basis for future research building on these findings. According to the authors, these studies establish the potential of direct retinal beta-amyloid plaque imaging in live subjects as a tool for early Alzheimer's disease diagnosis and prognosis, as well as assessment of therapies.

More information: Journal paper: dx.doi.org/10.1016/j.neuroimage.2010.06.020

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