ALZHEIMER’S DIAGNOSIS BY RETINA?

Imaging of retinal plaques may hold promise for assessing patients with Alzheimer’s

by Gearoid Tuohy

Researchers have found that non-invasive in vivo imaging of a hallmark of Alzheimer’s disease may be feasible through retinal imaging.

The researchers, led by Dr Maya Koronyo-Hamaoui and Dr Daniel L. Farkas at the Cedars-Sinai Medical Centre in Los Angeles, California, detected Ab plaques in post-mortem retinas of individuals suspected and confirmed to have Alzheimer’s disease. Once validated in the retinas of live Alzheimer’s patients, the technology may provide a significant clinical tool in assessing patients for diagnosis, monitoring and response to medical treatment.

According to the researchers, the current definitive diagnosis of Alzheimer’s disease is determined only after brain autopsy through the detection of b-amyloid peptides (Ab) and intercellular neuritic tangles. To date, research into non-invasive detection of Ab plaques in live Alzheimer’s patients has yet to yield tools of high resolution and specificity. An alternative approach suggested through the current study proposes direct optical imaging of the retina to detect Ab plaques.

The research, published in Neuroimage (Koronyo-Hamaoui, M et al, doi:10.1016/j.neuroimage.2010.06.020) reports the “presence of Ab plaques in retinas of post-mortem eyes from Alzheimer’s patients, and moreover, in retinas from those suspected as early-stage cases”. In addition, the research presents evidence for the formation of Ab plaques in the retina of Alzheimer’s animal models prior to their appearance of plaques in the brain. Accumulation of hallmark proteolytic products of amyloid precursor protein b-amyloid peptides (Ab) – have been widely documented to form extracellular aggregates termed Ab plaques in the neuronal tissues of Alzheimer’s patients. While non-invasive imaging of such Ab plaques remains clinically challenging and of limited resolution, an alternative approach to visualise such plaques through the retina by direct optical imaging may represent a valuable clinical tool in Alzheimer’s medicine. The value of such a tool would rest on the assumption that Ab plaques forming in patients’ retinas are similar to those that form in the brain. On that basis the researchers set about a series of experiments to test to what extent Ab plaques in the retina were relevant to those in the brain.

Curcumin staining First, the researchers used transgenic mouse models of Alzheimer’s to test the specificity of a natural and safe fluorochrome, “curcumin”, to bind and label Ab plaques. Following systemic injection of curcumin (7.5mg/kg/day), fluorochrome labelling was shown to be coincident with established anti-Ab monoclonal antibody labelling in the transgenic model brain tissue.

Curcumin staining, found in Alzheimer’s mouse models but not in wild type subjects, was shown to be present in several retinal locations including the nerve fibre layer, retinal ganglion cell layer, inner and outer plexiform layers and the inner nuclear layer. The bioavailability of the fluorochrome following systemic injection showed that the dye could readily cross the blood-brain and blood-retinal barriers. Ab plaques appeared to be detected in the retina but not the brain of transgenic models at 2.5 months which the authors interpreted as a suggestion that Ab plaques in the retina may precede their appearance in the brain. If such findings translate to human Alzheimer’s patients, an early diagnostic of Alzheimer’s could be developed further.

A key component of validating the relevance of Ab plaques in the retina to Ab plaques in the brain was to assess how both plaques responded to immunisation with an altered myelin derived peptide, previously shown to redistribute plaque burden in the brains of transgenic models. The researchers aimed to investigate if retinal plaques and brain plaques behaved similarly in response to the same therapy. Following delivery of the peptide, loaded on dendritic cells, (0.5X106 cells/200ul phosphate buffered saline) a substantial reduction of Ab plaque burden was observed in both retinal and brain tissues using curcumin staining.

The researchers advanced to applying curcumin staining on post-mortem eyes from patients who had been diagnosed with Alzheimer’s. Similar results and labelling patterns of retinal Ab plaques by curcumin were recorded in the human tissues and further, staining could also be detected in Alzheimer’s patients that were possibly at early stages of the disease.

Qualitative correlation The researchers observed “a qualitative correlation between the severities of the clinical diagnosis verified by post-mortem neuropathology and retinal Ab plaque burden”. They were also able to identify Ab plaques, which were specifically detected with curcumin, in the retinas from definite and suspected early Alzheimer’s patients.

In conclusion, the researchers proposed that the transgenic model data showed that Ab plaques could be detected in the retina before becoming visible in the brain and that the plaque burden correlated with the progression of brain pathology. The reduction in plaque size following immunisation provided further weight to support the hypothesis that retinal plaque pathology “faithfully represents the brain disease.”

Prior research into Alzheimer’s disease has suggested that neuropathological abnormalities may occur decades prior to a clear clinical manifestation. Such studies had identified abnormalities, including Ab plaques, at a prodromal phase of the disorder further under-scoring the clinical need for early diagnosis allowing for potentially earlier opportunities for medical intervention.

According to the researchers, their latest findings demonstrate the first proof for an amyloid plaque pathology in the retina that appears to be specific for Alzheimer’s disease. In addition, the study is thought to provide the first demonstration of Ab plaques in post-mortem retinas from suspected and definite Alzheimer’s patients that reflected Alzheimer’s brain pathology. As the detection occurred in the inner layers of the retina live imaging of this “accessible part of the brain” may be achievable through an improvement in currently available ophthalmic imaging tools. “Based on their unique size, signature and distribution within the retinas, Ab plaques observed in Alzheimer’s patients could be eventually used for differential diagnosis,” the researchers stated.

Journal Watch by Sean Henahan

Progress with biosynthetic cornea

Researchers from Sweden and Canada report remarkable results in a clinical study of biosynthetic cornea transplantation. A preliminary clinical trial involving 10 patients showed that biosynthetic corneas could help regenerate and repair damaged eye tissue and improve vision in humans. This is the first study to show that an artificially fabricated cornea can integrate with the human eye and stimulate regeneration. Patients did not experience any rejection reaction or require long-term immune suppression. The biosynthetic corneas also became sensitive to touch and began producing normal tears to keep the eye oxygenated. Vision improved in six of the 10 patients, and after contact lens fitting, vision was comparable to conventional cornea transplantation with human donor tissue. The promising clinical results are a culmination of more than a decade of work using synthetically cross-linked recombinant human collagen moulded into the shape of a cornea. The researchers report that further biomaterial enhancements and modifications to the surgical technique are ongoing, and new studies are being planned that will extend the use of the biosynthetic cornea to a wider range of sight-threatening conditions requiring transplantation.


Bio-Ophthalmology

Dr May Griffith displays a biosynthetic cornea that can be implanted into the eye to repair damage and restore sight.

Photo courtesy of the Ottawa Hospital Research Institute