GLAUCOMA

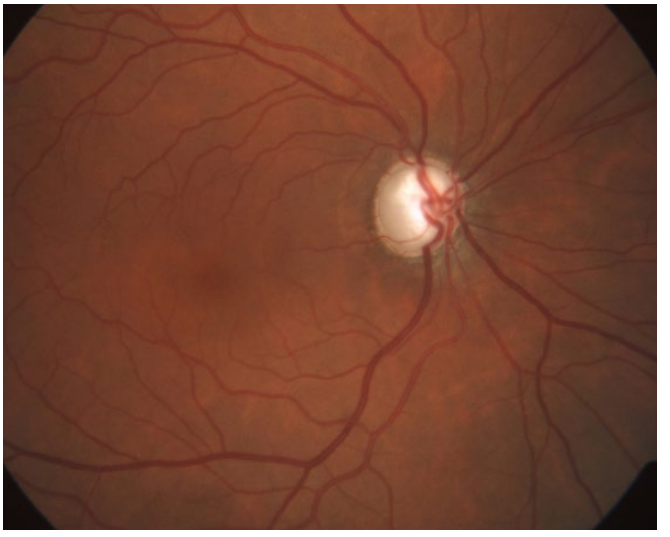
Systemic Drugs and POAG

A STUDY TO IDENTIFY ASSOCIATIONS between systemic medications and primary open-angle glaucoma (POAG) found that selective serotonin reuptake inhibitors (SSRIs), a common class of antidepressant medications, were associated with a 30% reduced risk of POAG. Conversely, calcium channel blockers, a common class of antihypertensive medications, were associated with a 26% increased risk of POAG.[1]

"These findings are so striking [that] they merit further research to help determine whether the association is causal. If so, this could significantly change how we manage glaucoma patients, particularly those with coexisting depression or hypertension," said Anthony P. Khawaja, PhD, FRCOphth, at Moorfields Eye Hospital in London.

A needle in a haystack. Drawing on a large insurance claims database covering Jan. 1, 2007, to Dec. 31, 2014, Dr. Khawaja and his colleagues identified more than 6,100 cases of POAG in patients who had undergone at least 1 glaucoma procedure. Cases were matched in a 1:5 ratio to 30,650 controls (defined as those who had undergone a cataract procedure but had no diagnosis of glaucoma).

The database identified 423 drug classes and 1,763 generic drugs that had been prescribed over a 5-year period prior to the glaucoma procedure or cataract surgery. "The huge sample size from this type of data meant we could test for associations with all known drugs and still find significant associations that survive correction for multiple testing," Dr. Khawaja said.



RETHINKING MANAGEMENT? *If the association with certain drug classes holds, patients with POAG (shown here) who are taking medications for depression or hypertension may need to be managed differently.*

Further findings from systemic drugs. In addition to the SSRI and calcium channel blocker findings, the following associations emerged:

- Beta-blockers showed the second most significant protective association, particularly the generic metoprolol succinate. (Ophthalmic beta-blockers were excluded from the study.)
- Serotonin-norepinephrine reuptake inhibitors (SNRIs) showed a weaker—but still significant protective—association than SSRIs.
- There was a clear dose-response relationship for SSRIs, with progressively lower odds of POAG as the days of drug supply increased.
- There was no evidence of a dose response for calcium channel blockers.

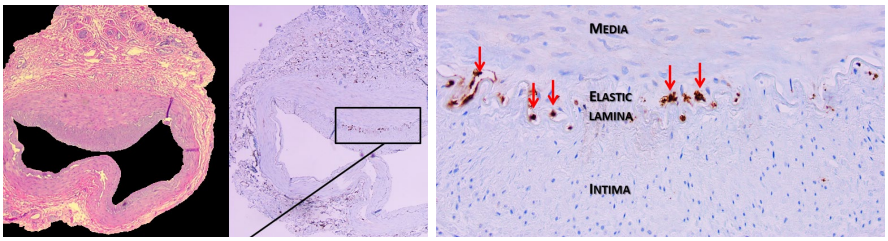
Affirmations and a surprise. The association between calcium channel blockers and an increased risk of POAG corroborated a finding in the Rotterdam Study.[2] "This is not a well-known association, but it is potentially very important, given the number of glaucoma patients on antihypertensive drugs," Dr. Khawaja said. "Calcium channel blockers have even been suggested as potential treatments for glaucoma, so to clarify this relationship with further research [will be] very important."

Given the known effects of beta-blockers on intraocular pressure, the beta-blocker finding was also not surprising. Rather, it validated the study design, Dr. Khawaja said. It also bolstered the credibility of the SSRI association, which has not been previously reported. As 22% of controls and 16% of cases were prescribed SSRIs, the association, if causal, could have a potential impact on POAG prevalence, he said.

Now Dr. Khawaja is looking for associations in other datasets. "If we replicate these findings and better characterize these associations, then further work leading toward possible pharmacological modifications of glaucoma risk will be warranted," he said. "We are many steps away, but it is conceivable that a trial of SSRIs to slow progression

of disease in POAG patients is warranted in the future." —*Miriam Karmel*

1 Zheng W et al. *Ophthalmology*. 2018;125(7):984-993.
2 Müskens RP et al. *Ophthalmology*. 2007;114(12):2221-2226.
Relevant financial disclosures—Dr. Khawaja: Novartis: C.



COMPARISON. *Routine hematoxylin and eosin (HE) stain of a histopathologic section of a temporal artery (left) shows irregular intima hyperplasia but no discrete multinucleated giant cells. Immunohistochemistry using CD68 antibody discloses positive cells at the level of the elastic lamina located in the media (muscularis) side with at least 5 positive cells (center and right, arrows).*

NEURO-OPHTHALMOLOGY

New Metric for Determining GCA Prognosis

WHICH GIANT CELL ARTERITIS (GCA) patients might benefit from early treatment with agents other than conventional steroid therapy?

A recent study offers a quantitative approach to answering that question.[1]

In this retrospective study, researchers assessed 42 GCA patients who had undergone temporal arterial biopsies (TABs), the gold standard for GCA diagnosis, at Houston Methodist Hospital in 2015.

The researchers reviewed patient charts for 4 variables: recurrence, number of days on glucocorticoids, referral to a rheumatologist, and placement on immunomodulatory therapy (IMT). They then correlated patients with features of healing/treated GCA and the 4 variables to the CD68 macrophage immunohistochemical marker found

CORNEA

Hyaluronic Acid Film Speeds Corneal Healing

PRECLINICAL TESTING OF A NOVEL HYDROGEL FILM made from cross-linked hyaluronic acid (HA) suggests that the polymer can rapidly accelerate the healing of large corneal burns, re-epithelializing them by 48 hours after the film is placed into the inferior fornix.[1]

Rapid recovery. The study, conducted in New Zealand white rabbits, found that corneas treated with the film, made of cross-linked, thiolated hyaluronic acid (CMHA-S), achieved complete re-epithelialization at 48 hours. In contrast, untreated eyes never had complete epithelial regrowth during 14 days of follow-up. The researchers found that both groups experienced some regression of epithelialization by the end of the study. However, the treated group retained significantly better re-epithelialization—83% versus 63% for untreated eyes.

Other findings. The treated eyes showed a 50% reduction in area of corneal opacity at the 14-day mark, while the untreated eyes had a 16% reduction. In addition, the treated eyes had significantly less edema, possibly because the compound inhibited the release of inflammatory mediators and cytokines.

Method of action. The cross-linking of CMHA-S into a translucent film enables the HA, long known for its protectant and lubricating properties, to be released slowly over time and to persist longer in the eye than a non–cross-linked liquid HA drop would, said Barbara Wirostko, MD, with EyeGate Pharmaceuticals and based in Salt Lake City.

"The film remains intact and in place longer than eyedrops and is less likely to break down. Thus, it may promote wound healing over an extended time period, especially in cases of severe trauma," she said. In the rabbit study, the film remained intact in the fornix for at least 14 days.

From animals to humans. A CMHA-S gel formulation has been available for several years as a treatment for dry eye and corneal wounds in animals (Remend, Bayer Animal Health), and EyeGate is developing it for use in humans, Dr. Wirostko said. In a pilot clinical study, post-PRK epithelial defects treated with the gel were, on average, 29% to 36.9% smaller as early as postop day 1 than those in eyes managed with a bandage contact lens and artificial tears.[2]

The company also is exploring the possibility that CMHA-S film can be used as a carrier for therapeutic molecules such as antibiotics. Dr. Wirostko said that this capability has already been demonstrated preclinically. "The film provides an alternative way of delivering the hyaluronic acid polymer and potential therapeutics in a sustained-released manner in severely traumatized eyes, potentially reducing or eliminating the frequent use of eyedrops." —*Linda Roach*

1 Griffith GL et al. *Burns*. 2018;44(5):1179-1186.
2 Durrie DS et al. *J Cataract Refract Surg.* 2018; 44(3):369-375.
Relevant financial disclosures—Dr. Wirostko: EyeGate: E,O.

Patricia Chévez-Barrios, MD

on the TAB specimens.

Slice metric. Using a metric of CD68+ cells per histologic slice, they found the following:

- Patients whose symptoms recurred at least once during follow-up had a greater number of CD68+ cells per slice compared to those with no recurrence (2.40 vs. 1.13, respectively).
- There was no statistical difference in cells/slice between patients who were referred to rheumatology and those who were not.
- Patients eventually placed on IMT had a greater number of cells/slice than did those who did not receive IMT (5.00 vs. 1.21, respectively).

"In this study, patients who had a more severe disease course [necessitating being placed on IMT] had a statistically significant greater number of CD68+ cells per slice than those patients not placed on IMT," said Patricia Chévez-Barrios, MD, at Houston Methodist Hospital.

A surprise. As for time on glucocorticoids, the researchers had hypothesized that the number of CD68+ cells/slice would decline over the course of treatment. In fact, there was no correlation between cells/slice and length of time on glucocorticoids, even beyond 40 days following initial treatment.

Clinical implications. Since most patients are on glucocorticoids at the time of TAB, quantification of CD68+ cells in TAB may help to identify patients with recalcitrant disease who cannot be managed with steroids alone, Dr. Chévez-Barrios said.

She suggested that pathologists could employ the metric to aid in determining severity of the disease course. "If the patient has an increased number of CD68+ cells per slice—greater than 2 cells per slice—then the patient might need to be referred for rheumatologic treatment sooner than a patient who has fewer than 2 cells per slice."

—Miriam Karmel

1 Sultan H et al. *Am J Ophthalmol.* Published online June 8, 2018.

Relevant financial disclosures—Dr. Chévez-Barrios: None.

RETINA

Thin RNFL Linked to Increased Risk of Dementia

THE LIST OF FAILED DRUG TRIALS for Alzheimer disease (AD) is lengthy and continues to grow, mainly because patients receiving treatment have an advanced case of the disease. Early detection is, therefore, key to finding a cure. But can an eye screening test help identify risk? A team of U.K. researchers explored the connection between the retina and dementia and found that a thin retinal nerve fiber layer (RNFL) might indicate future cognitive decline.[1]

The association. UK Biobank is a multicenter, community-based study of more than 30,000 U.K. residents aged 40 to 69 years. At enrollment, participants underwent optical coherence tomography (OCT) imaging, a physical examination, and cognitive testing. The research team found that worse cognitive performance was associated with a thinner RNFL at baseline, and those in the thinnest quintile of RNFLs were 11% more likely to fail at least 1 cognitive test. In addition, participants with an RNFL thickness in the 2 thinnest quintiles were almost twice as likely to have at least 1 test score be worse at follow-up.

Treatment implications. "Our findings suggest the retinal abnormalities that are identifiable in established dementia begin to manifest in the early stages of cognitive decline," said coauthor Paul J. Foster, PhD, FRCOphth, at Moorfields Eye Hospital and UCL Institute of Ophthalmology in London. And the earlier the detection, the better, he added. "Between 2002 and 2012, 99% of clinical trials of treatments for AD failed. A probable reason for this failure rate is that treatments are being provided to those patients who already have irreparable damage to the brain. By targeting people in the very early stages of cognitive change, it should be possible to design better clinical trials for treatments" that slow or stop further onset.

Supporting evidence. Similar results emerged in a Dutch study that explored the link between retinal neurodegeneration and dementia.[2] In the more than 5,000 study participants, OCT imaging showed that thinner ganglion cell–inner plexiform layers were associated with existing dementia, while thinner RNFLs were associated with an increased risk of developing dementia.

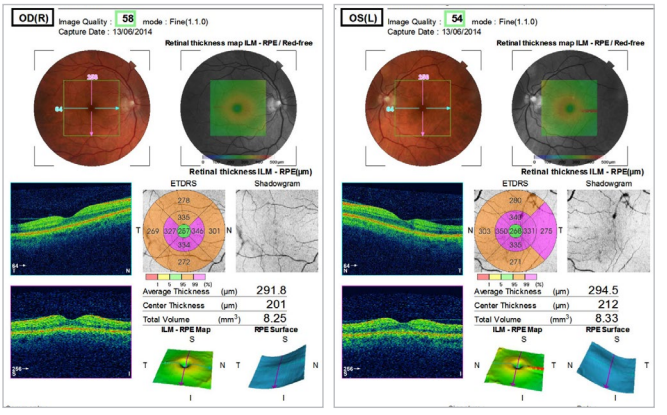
Taken together, these 2 studies suggest that retinal abnormalities—and possibly other ocular characteristics—may serve as unique preclinical biomarkers for dementia, specifically for AD. For clinicians and researchers, this could present an opportunity in the future to use OCT as an accessible and noninvasive tool to help monitor disease progression, evaluate treatment response, and shape eligibility determination for future clinical trials.

—Michael Mott

1 Ko F et al. *JAMA Neurol.* Published online June 25, 2018.

2 Mutlu U et al. *JAMA Neurol.* Published online June 25, 2018.

Relevant financial disclosures—Dr. Foster: None.



BIOMARKER. *This OCT map shows a thin RNFL, a potential red flag for dementia.*

Paul J. Foster, PhD, FRCOphth

See the financial disclosure key, page 8. **For full disclosures,** including category descriptions, view this News in Review at aao.org/eyenet.