MAYO CLINIC

Ophthalmology Update

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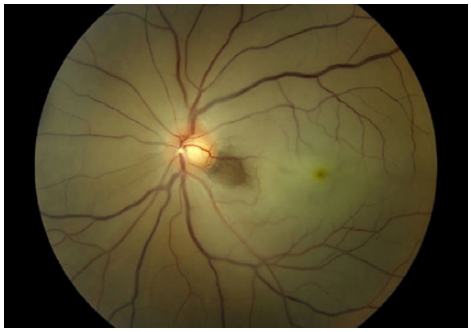

Figure. An acute central retinal artery occlusion.

New Study Assesses the Risk of Stroke Before and After Central Retinal Artery Occlusion

Central retinal artery occlusion (CRAO) affects 1 to 2 out of every 100,000 people each year, with 80% of patients experiencing a final visual acuity of 20/400 or worse. CRAO causes acute vision loss in the affected eye or eyes due to inner retinal ischemia (Figure).

In addition to identifying debilitating vision loss, studies from Taiwan and Korea, published in the *American Journal of Ophthalmology* in 2012 and *Ophthalmology* in 2015, respectively, also suggest that retinal artery occlusions are associated with an increased risk of ischemic stroke. Mayo Clinic researchers sought to further evaluate this risk.

"We recently looked at patients treated at Mayo Clinic and found that there was a 5% risk of symptomatic ischemic stroke within two weeks of CRAO. However, there can potentially be bias toward more-severe disease when looking at a tertiary center such as Mayo Clinic," says John J. Chen, M.D., Ph.D., a neuro-ophthalmologist at Mayo Clinic in Rochester, Minnesota. "Therefore, the goal of this study was to evaluate the risk of stroke at the time of a CRAO using a population-based cohort — via the Rochester Epidemiology Project — to help guide the discussion on how quickly a comprehensive cerebrovascular evaluation and work-up should take place in patients with CRAO."

This study assessed the risk of stroke, transient ischemic attack (TIA) and transient monocular vision loss (TMVL) in the 15 days before and after CRAO using the Rochester Epidemiology Project. Eligible participants were over 18 years old and had a CRAO while living in Olmsted County, Minnesota, between January 1, 1976, and September 9, 2016.

METHODOLOGY

The purpose of this study was to analyze population-based data to study the correlation between CRAO and incidence of stroke. Patient charts were reviewed retrospectively. Information gathered included:

- Patient gender
- CRAO laterality
- Age at diagnosis
- Cause of CRAO
- Ischemic or hemorrhagic stroke within 15 days before or after CRAO
- TIA within 15 days before or after CRAO
- TMVL within 15 days before or after CRAO

The study was published in *Ophthalmology,* the journal of the American Academy of Ophthalmology.

John J. Chen, M.D., Ph.D.

Kevin D. Chodnicki, M.D.

Systemic comorbidities were identified and visual acuity was measured at initial presentation of CRAO and one year following the diagnosis. The median age of participants was 76 years, 56.2% were male and 89.9% were white.

Racial demographic discrepancies can limit the general applicability of study results, and there are challenges in reviewing retrospective data, particularly when a study spans several decades, because there are changes in diagnostic evaluations, treatment, follow-up and technological advancements over time. However, this study has the benefit of being population based. Its results therefore avoid the potential referral bias that can occur in tertiary centers.

"It is important for clinicians, health care leaders and the public to understand the implications of CRAOs not only for vision but for neurological health and stroke as well. We hope these results can help inform the discussion as standards of care are optimized for the management of CRAO," says Kevin D. Chodnicki, M.D., a neuro-ophthalmologist and assistant professor of ophthalmology at Mayo Clinic in Rochester, Minnesota.

RESULTS

Among 89 study participants with CRAO, 3.4% had a stroke the same day or within 15 days after CRAO, with 2.2% having ischemic strokes and 1.1% having hemorrhagic strokes. The occurrence of these strokes indicates a significant increase when compared with the anticipated number of strokes over a 30-day period using age- and gender-specific stroke incidence rates for Olmsted County.

"This population-based study confirms that there is a small increased risk of symptomatic stroke around the time of a CRAO, which makes sense because the pathophysiology for both CRAO and CNS stroke is usually thromboembolic disease," Dr. Chen explains.

According to this study, the risk of symptomatic ischemic stroke is 2.2% in the 15 days before and after a CRAO within a population-based cohort. This risk is slightly lower than that of most other studies from tertiary centers. The study's data can be used in the discussion of standards of care for the work-up, management and treatment of people with acute CRAO.

FOR MORE INFORMATION

Chang Y. S., et al. Retinal artery occlusion and the 3-year risk of stroke in Taiwan: A nationwide population-based study. *American Journal of Ophthalmology*. 2012;154(4):645.

Park S. J., et al. Risk and risk periods for stroke and acute myocardial infarction in patients with central retinal artery occlusion. *Ophthalmology*. 2015;122(11):2336.

Chodnicki K. D., et al. Stroke risk before and after central retinal artery occlusion: A population-based analysis. *Ophthalmology*. 2022;129(2):203.

Drusen Phenotypes Associated With Advanced Age-Related Macular Degeneration

Reticular pseudodrusen (RPD), basal laminar drusen (BLD) and especially calcified drusen (CaD) were associated strongly with advanced age-related macular degeneration (AMD) in a cross-sectional study of a large group of eye bank eyes selected from a population at risk of AMD.

"AMD is a leading cause of blindness in many diverse, global populations. No treatments currently exist for geographic atrophy (dry AMD) or unresponsive exudative AMD (wet AMD). Both are part of end-stage AMD," says Timothy W. Olsen, M.D., an ophthalmologist at Mayo Clinic in Rochester, Minnesota. "Specific drusen phenotypes have been shown to represent diagnostically relevant risk factors for progression to advanced stages of AMD (Figure, see page 3). Our intent in this study was to stage maculopathy, assess and quantify drusen, determine drusen subtype frequency, and compare drusen subtypes with age-related AMD stage and cause

of death." The study was published in *Ophthalmology Retina* in 2021.

CLINICAL CHARACTERISTICS AND EVALUATION

Eye bank personnel procured donor eyes for research and obtained at-risk donors for AMD by prioritizing eyes of donors over 65 years old. Dr. Olsen and eye bank personnel recorded donor characteristics including age, race, sex, and time and cause of death, along with a limited medical and ocular history. Globes were procured at a mean of 12 hours after donor death.

Researchers used the Minnesota Grading System (MGS) to obtain images from 2,092 eye bank eyes donated by 1,067 donors between January 2005 and August 2020. Ultimately, 1,777 eyes formed the database and both the four-step and nine-step MGS criteria were applied.

The four-step MGS criteria are based on drusen size, type of drusen, presence of pigmentary changes, and geographic atrophy or exudative AMD, or both. The four steps indicate disease-free versus early, intermediate and advanced stages of AMD. "The nine-step MGS criteria allow for more granular AMD staging by quantifying total drusen area, pigmentary changes and areas of atrophy," says Dr. Olsen. "The MGS links directly to the Age-Related Eye Disease Study, or AREDS, the largest human database on AMD progression, and thus translates clinical risk to MGS score." The Age-Related Eye Disease Study was published in the *American Journal of Ophthalmology* in 2001.

Researchers analyzed the association between each drusen subtype group and known cause of death, tabulated per person and classified as cardiovascular, neoplastic, infectious (such as pneumonia), and other (such as renal failure, intestinal bleeding or trauma).

In both the four-step and nine-step MGS, eyes with each drusen subtype were associated independently and significantly with more-advanced stages of AMD:

- RPD frequency was 13% (228 eyes); mean donor age was 80 years
- BLD frequency was 7% (131 eyes); mean donor age was 80 years
- CaD frequency was 5% (84 eyes); mean donor age was 84 years

CaD was more prevalent in older donors (80 years older on average) and showed a strong association with advanced disease. "Our laboratory established the four-step and nine-step MGS. Both use the specific phenotype definitions from the AREDS applied to eye bank eyes," notes Dr. Olsen. "A key advantage of using an eye bank model is that postmortem eyes also can be graded for the presence of visible RPD, BLD and CaD, thus allowing determination of associations for each entity with AMD stage and cause of death." The AREDS includes more than 70 publications that characterize the clinical course of AMD from living patients.

RPD AND CARDIOVASCULAR DEATH

"We found that RPD, BLD and CaD all showed a strong association with more-advanced stages of AMD, but interestingly, we also identified a potential association of RPD and cardiovascular death," says Dr. Olsen. "We propose a mechanistic hypothesis for such an association: RPD may represent an ophthalmologic biomarker for coronary artery disease."

"Our prior studies, which used cytologic analysis of MGS-graded donor tissue at the National Institutes of Health, have shown a similar chronic inflammatory pathway, possibly involving tissue macrophage polarization — either primary or secondary — that may be involved in the development of pathologic vascular endothelial plaques in coronary artery disease, as well as in the generation of RPD."

FOR MORE INFORMATION

Mano F., et al. Association of drusen phenotype in age-related macular degeneration from human eye-bank eyes to disease stage and cause of death. *Ophthalmology Retina.* 2021;5(8):743.

The Age-Related Eye Disease Study Research Group. The age-related eye disease study system for classifying age-related macular degeneration from stereoscopic color fundus photographs: the age-related eye disease study report number 6. *American Journal of Ophthalmology.* 2001;132(5):668.

Timothy W. Olsen, M.D.

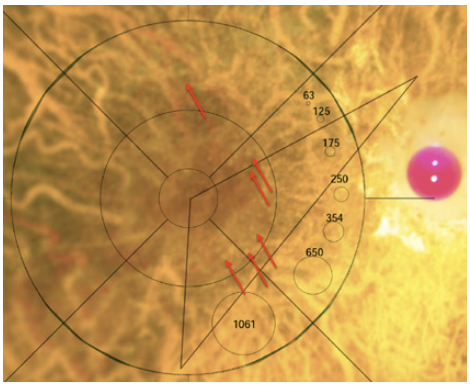

Figure. This is a color image from the back of the eye (posterior pole) from an eye bank donor who died of coronary artery disease. The donor has high-risk drusen (red arrows). The specific drusen subtype is referred to as reticular pseudodrusen (RPD). In our study, we found a statistically significant association of RPD with a cardiac cause of death. The grid patterns are placed in each fundus photograph and were adopted from the National Institutes of Health/ National Eye Institute Early Treatment Diabetic Retinopathy Study grading template, centered on the macula or the retinal center of vision. The red circle is a ruby sphere that is used as a size reference for the grid and measures 1,000 microns in diameter. The smaller circles are each different size references used to quantify drusen. Note that the neurosensory retina has been removed to allow visualization of the drusen. The image is provided courtesy of the Lions Eye Institute for Transplant and Research.

Coming Soon: Ophthalmology Podcast

Erick D. Bothun, M.D.

Andrea A. Tooley, M.D.

Mayo Clinic Ophthalmology Podcast, hosted by Erick D. Bothun, M.D., and Andrea A. Tooley, M.D., covers the latest and greatest in ophthalmology through the lens of an academic institution — Mayo Clinic. Expert guests from around the world discuss ophthalmology and various subsets of the specialty.

Dr. Bothun is a Mayo Clinic pediatric eye surgeon who cares for children of all ages with eye diseases. Dr. Bothun specializes in diagnosing, treating and researching complex cataracts in infants and children. He leverages his expertise and research experience in pediatric cataracts to tailor the surgical and clinical treatment for each child. Dr. Tooley specializes in ophthalmic plastic and reconstructive surgery. Her clinical and surgical interests include skull base and orbital tumors, endoscopic orbital surgery, aesthetic facial rejuvenation, facial trauma, and facial reconstruction.

Contact Us

Mayo Clinic welcomes inquiries and referrals, and a request to a specific physician is not required to refer a patient.

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Educational Opportunities

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Ophthalmology Update

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Cover Image
Human multicolored iris of the eye animation concept. Credit: CG Alex

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