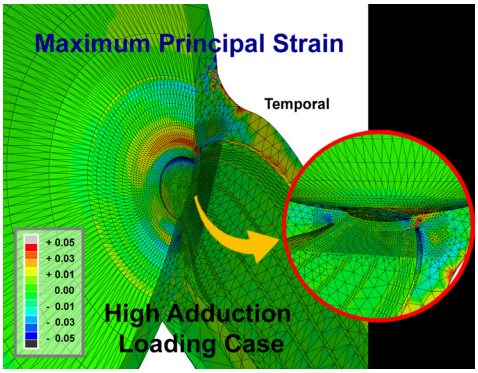
UCLA Stein Eye Institute | DOHENY EYE INSTITUTE

CLINICAL UPDATE

Repetitive Strain Injury to the Optic Nerve Could Play an Important Role in Some Glaucoma Cases



Computer simulation, by finite element analysis, of mechanical strain in the optic nerve head and adjacent eye wall caused by tethering of the optic nerve sheath during adduction eye movement. This simulation incorporates a combination of biomechanical properties—all measured in tissues donated to eyebanks—that are predicted to result in glaucomatous optic nerve damage over a lifetime of eye movements. (Credit: simulation and graphic by Joseph Park, MS, using data collected by Andrew Shin, Joseph Park, and Joseph L. Demer.)

It has been long believed that glaucoma is caused by damage to the optic nerve due to elevated intraocular pressure. But that may not be the case for many people who have glaucoma. "In Western populations, as many as half of people with glaucoma have intraocular pressure in the normal range, and in certain Asian populations, approximately 90 percent have normal pressure," says Joseph Caprioli, MD, David May II Chair in Ophthalmology and chief of the Glaucoma Division at the UCLA Stein Eye Institute. Because of that, Dr. Caprioli notes, intraocular pressure is now considered a glaucoma risk factor, but not a defining characteristic.

Stein Eye Institute researchers are investigating a new concept with major implications for the second-leading cause of blindness worldwide: the possibility that many cases of glaucoma can be attributed in part to repetitive strain injury to the optic nerve caused by everyday eye movements. "If this turns out to be the case, it could be a major breakthrough," says Joseph L. Demer, MD, PhD, Arthur L. Rosenbaum, MD, Chair in Pediatric Ophthalmology, chief of the Pediatric Ophthalmology and Strabismus Division, and director of the Ocular Motility Clinical and Basic Science Laboratory. Dr. Demer is also leading a National Eye Institute-funded research team that includes Dr. Caprioli and his Glaucoma Division colleagues. "Currently, intraocular pressure is the only significant modifiable risk for

continued on page 2

Importance of Eye Screening Exams for Newborns at Risk for Zika Virus Infection

A high-profile research effort by the UCLA Stein Eye Institute, other UCLA departments, and counterparts in Rio de Janeiro, Brazil, has produced some of the strongest evidence to date that all infants potentially exposed to the Zika virus during gestation should undergo screening eye examinations, given that eye abnormalities can be the only initial finding in congenital Zika virus infection.

The spread of the mosquito-borne Zika virus emerged as a public health crisis in Brazil in 2015 and 2016, just as the country was set to host the 2016 Olympics. Brazil's health ministry declared an end to its emergency in early 2017, but both the ministry and the World Health Organization have warned that while there are now many fewer new infections, Zika hasn't disappeared and a future outbreak is a possibility. Other mosquito-borne

continued on page 3

June 2018
Vol.27 | No.1

In This Issue

Repetitive Strain Injury to the Optic Nerve Could Play an Important Role in Some Glaucoma Cases

continued from cover

glaucoma, but most cases of glaucoma in the world today occur at normal, not elevated, pressure."

During the course of his research using magnetic resonance imaging (MRI) to learn about eye muscle function, Dr. Demer began to hypothesize that the types of eye movements people make tens of thousands of times a day—such as when reading, glancing, or changing their gaze—might contribute to some cases of glaucoma. "We would have our volunteers make large eye movements as they were undergoing scanning, and we noticed there are certain gaze positions where the optic nerve isn't quite long enough to allow the eye to rotate freely without it tightening," he says. The most notable of these positions is adduction, in which the eye rotates inwardly toward the nose. "In almost everyone, that causes the optic nerve to use up all of its available slack and become tight, pulling on the back of the eye," Dr. Demer explains. "We recognized from MRI that these movements impose a great deal of strain on the junction of the highly mobile eyeball with the optic nerve, which is the cable that conveys vision to the brain."

This is significant, Dr. Demer notes, because that junction—called the optic disc or optic nerve head—is the point where glaucoma damage is known to occur. "The site of the most common damage that we see is on the temporal edge of the optic disc, which is the edge that gets most tightly pulled when the eye rotates inwardly toward the nose," Dr. Demer says. "As someone who has followed patients for decades over the entire age range, I have seen that as people get older, the optic nerve head changes in appearance. Most patients develop a depression in the center that increases in size, and the nerve head tilts in the direction where these forces are pulling. Over time, the edge of the eye wall adjacent to the optic disc begins to atrophy in a crescent-shaped pattern in the majority of people."

To test the plausibility that these changes are results of the accumulation of wear and tear from adduction eye movements, Dr. Demer's team used a technique called finite element analysis, which is used by mechanical engineers to calculate how certain stresses will affect small elements in structures. In the finite element model, which is run on a supercomputer system at UCLA, the researchers rotated the eye beyond the point where the optic nerve ran out of slack, and found that this commonly encountered additional rotation produced stresses and strains in the places that commonly show clinical damage with age—particularly in patients who have glaucoma at normal intraocular pressure.

Next, the Stein Eye Institute researchers used a state-of-the-art imaging technique called optical coherence tomography (OCT) to view the eye over a range of gaze positions. They found that the optic nerve head rocks back and forth as the eye rotates, most notably in the adduction position. "This confirmed our prediction from MRI that optic nerve tethering should cause visible distortion," Dr. Demer says. "And in fact, the amount of distortion of the optic nerve tissues that we can see with OCT is far greater during adduction than it is when intraocular pressure is elevated during an acute attack of glaucoma."

Following up on these observations, Dr. Demer's group conducted a clinical study of glaucoma patients who have normal intraocular pressure, comparing them with a control group of healthy volunteers of comparable ages and another group of patients who have strabismus but not glaucoma. Of the three groups, only the glaucoma patients showed substantial eyeball retraction during adduction movements.

Then, looking at the microanatomy of the tissues from anatomical donations, the researchers found that in some older people, the optic nerve sheath thickens and stiffens, much like the sclerosis that occurs in the arteries. "What we are finding is that when the optic nerve pulls up tight in younger people, it harmlessly stretches without applying excessive force to the back of the eye," Dr. Demer explains. "But as some people get older and the sheath becomes less elastic, the eye gets pulled back into the socket, and the optic nerve head is deformed."

Dr. Demer and his collaborating team of glaucoma surgeons, bioengineers, anatomists, and UCLA undergraduate students are continuing to test their hypothesis. They have established a biomechanics laboratory, and using eye bank tissue that was provided by donors with and without glaucoma, they are measuring the elasticity and viscosity of various parts of the human eye. They are combining that work with microscopic analysis of the connected tissues in the same eyes in an effort to correlate the microscopic appearance and chemical composition of the tissues with their mechanical behavior. In addition, they are testing the clinical implications in larger groups of patients.

The research team is also studying the potential connection between the tethering of the optic nerve and the elongation of the eye that is characteristic of myopia (nearsightedness). "The glaucomatous condition of the optic nerve seems to be more prevalent and important in myopia," Dr. Caprioli says. "This might explain the extra glaucoma risk conferred by myopia."

Overall, Dr. Caprioli notes, "this work, if confirmed, would add an important risk factor for glaucoma that could lend itself to treatment."

Importance of Eye Screening Exams for Newborns at Risk for Zika Virus Infection

continued from cover

illnesses, such as dengue fever and yellow fever, tend to cycle periodically in accordance with mosquito breedings and other factors.

Irena Tsui, MD, assistant professor of ophthalmology at the Stein Eye Institute who is involved in the research, notes that the majority of people who carry the Zika virus are asymptomatic. "The danger is for pregnant women who have the virus," Dr. Tsui explains. "They may not know they have it, but there can be severe consequences to the fetus, including microcephaly and developmental delays, other profound neurological abnormalities, and ophthalmological problems that include blindness from retinal scarring and optic nerve hypoplasia."

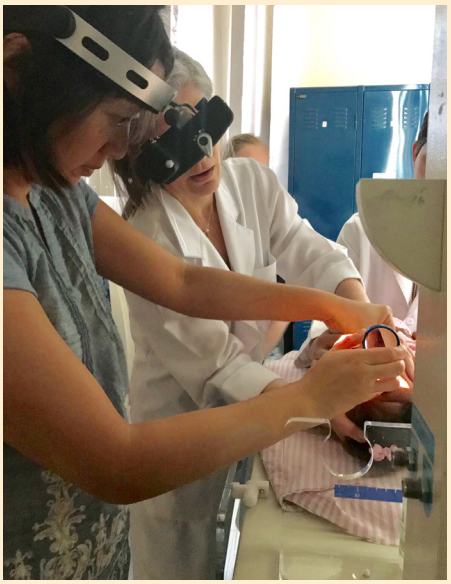
The team from UCLA and Rio de Janeiro came together at the height of the Zika epidemic in Brazil. The ophthalmology group in Rio de Janeiro is led by Andrea Zin, MD, PhD, a prominent pediatric ophthalmologist from the Instituto Fernandes Figueira—a Ministry of Health referral center for high-risk pregnancies and infectious diseases in children. In addition to Dr. Tsui, the UCLA group includes an infectious disease specialist and an obstetrician/gynecologist, each of whom has counterparts in Brazil.

Together, they examined a cohort of nearly 300 infants born during the epidemic who were known to be at high risk of having acquired the virus, in an effort to describe the full spectrum of ophthalmic disorders associated with congenital Zika virus infection in infants and its association with the timing of prenatal exposure and development of central nervous system problems. In addition to distinguishing Zika-related findings from eye findings of other endemic infections, the group set out to determine the rate of ophthalmic disease present in high-risk infants born where Zika was highly endemic at the time of pregnancy.

Dr. Tsui notes that the team from UCLA and Brazil is uniquely positioned to study the ophthalmic manifestations of congenital Zika virus infection given its rich database of biological specimens and clinical data on more than 400 pregnant women with suspected Zika virus infections, as well as on Zika-exposed infants from the time of birth. Moreover, the research team is distinguished by its use of polymerase chain reaction (PCR) testing to confirm the presence of Zika. "The available laboratory tests to confirm Zika are not always reliable because they cross-react with dengue, which is endemic to that area," Dr. Tsui explains. "PCR is a more definitive test, but it has to be done during the active window of infection—within the first week or so. We were the first group in the world with the opportunity and resources to do that kind of Zika testing, and that has drawn a great deal of attention to our research."

In their article, "Screening Criteria for Ophthalmic Manifestations of Congenital Zika Virus Infection," published in *JAMA Pediatrics*, Dr. Tsui and her colleagues reported on the eye findings of 112 infants whose mothers had PCR-confirmed Zika virus infection during pregnancy. They found that 21 percent of the infants had eye abnormalities—retinal pigment epithelial mottling, retinal scarring, optic nerve atrophy, and/or optic nerve hypoplasia. The researchers concluded that since ophthalmic manifestations may be the only initial findings in congenital Zika virus infection, all infants with potential exposure should undergo screening eye exams, regardless of whether there are central nervous system abnormalities. "Our findings suggest that there should be universal eye screening in areas where Zika is endemic," Dr. Tsui says.

> "By knowing earlier which infants test positive for Zika virus we can try to optimize function by starting vision therapy early, as well as recommending therapy for the potential developmental and neurological delays."



Dr. Irena Tsui (left) and Dr. Andrea Zin in Rio de Janeiro, Brazil, examining the retina of an infant with Zika-related eye findings.

Current guidelines in Brazil call for screening eye exams only for infants with microcephaly or laboratory-confirmed Zika virus infection. "There is no cure, and we can't change the scarring, but by knowing earlier which infants test positive we can try to optimize function by starting vision therapy early, as well as recommending therapy for the potential developmental and neurological delays," Dr. Tsui says. She notes that the UCLA team plans to continue traveling to Rio de Janeiro on a regular basis to help follow the children in the cohort as they age: "For research purposes, as we seek to better understand the virus and develop a cure, it is critical to collect this data and learn about long-term outcomes."

UCLA Stein Eye Institute | DOHENY EYE INSTITUTE

405 Hilgard Avenue
Box 957000, 100 Stein Plaza
Los Angeles, California 90095-7000

UCLA Stein Eye Institute
Westwood
100 Stein Plaza UCLA
Los Angeles, CA 90095
Referral Service: (310) 794-9770
Emergency Service: (310) 825-3090
After-Hours Emergency Service: (310) 825-2111
Website: uclahealth.org/eye

UCLA Stein Eye Center
Santa Monica
1807 Wilshire Blvd., Suite 203
Santa Monica, CA 90403
Phone: (310) 829-0160

Doheny Eye Center UCLA
Arcadia
622 W. Duarte Rd., Suite 101
Arcadia, CA 91007
Phone: (626) 254-9010

Doheny Eye Center UCLA
Orange County
18111 Brookhurst St., Suite 6400
Fountain Valley, CA 92708
Phone: (714) 963-1444

Doheny Eye Center UCLA
Pasadena
625 S. Fair Oaks Blvd., 2nd Floor
Pasadena, CA 91105
Phone: (626) 817-4747

Stein Eye Continuing Education Programs and Grand Rounds

For information, or to add your name to our distribution list, contact the Office of Academic Programs at (310) 825-4617, visit our website at uclahealth.org/eye, or email ACProg@jsei.ucla.edu.

STEIN EYE INSTITUTE

CLINICAL UPDATE

JUNE 2018
VOL. 27 I NO.1

DIRECTOR
Bartly J. Mondino, MD

MANAGING EDITOR
Tina-Marie Gauthier

CONTRIBUTOR
Dan Gordon

DESIGN
Hada-Insley Design

For inquiries about *Clinical Update*, contact Stein Eye Institute Managing Editor, Tina-Marie Gauthier, at gauthier@jsei.ucla.edu.

The Stein Eye Institute is a proud affiliate of the Doheny Eye Institute.