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Glaucoma Care on the Cutting Edge

Proceedings of the
Seventh Annual Scientific Meeting
of the Optometric Glaucoma Society

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INTRODUCTORY REMARKS

We are excited to bring you the Proceedings from the Seventh Annual Meeting of the Optometric Glaucoma Society (OGS), held in Anaheim, Calif., October 20 to 22, 2008. This year's meeting ran over three days, including the joint session with the Glaucoma Progression Scholars, an affiliation of researchers and clinicians with a common interest in glaucoma progression.

In this year's program, we covered a wide spectrum of topics, yet focused on what is new and cutting edge in each. Topics included epidemiology of glaucoma, patient communication, the relationship between visual fields and everyday functioning, and expanding uses of optical coherence tomography. Other lectures discussed how determining patients' rates of progression might help one identify those at risk of visual loss. Researchers also discussed the apparent dissociation between structural and functional progression.

The 2008 Honoree, Robert Ritch, MD, FACS, FRCOphth, in his lecture "Exfoliation Syndrome: Beyond the Eye," explained how exfoliation syndrome (XFS) is a systemic disorder, with glaucoma as the ocular manifestation. XFS is increasingly associated with cardiovascular and cerebrovascular diseases as well as other systemic disorders, such as Alzheimer's disease. Dr. Ritch also discussed milestone research that showed that two common single nucleotide polymorphisms are associated with XFS and exfoliative glaucoma.

In the 2008 President's Lecture, Theodore Krupin, MD, explained how the definition of glaucoma has evolved so that elevated intraocular pressure no longer represents glaucoma itself, but is just one risk factor. Population-based studies suggest that low-pressure glaucoma represents some 20% to 39% of cases of open-angle glaucoma in the United States. Dr. Krupin also offers an update on the Low-Pressure Glaucoma Treatment Study (LoGTS), a triple-masked randomized trial that will compare the efficacy of brimonidine vs. timolol to alter the course of low-pressure glaucoma as measured by the rate of progression of visual field loss.

I would like to thank the speakers who took time from their busy schedules to share their wisdom with members and guests. I would especially like to thank Brad Fortune, OD, PhD, 2008 OGS Program Chair, as well as John McSoley, OD, and Michael Sullivan-Mee, OD, 2008 meeting co-chairs. I would also like to thank John Flanagan, MCOptom, PhD, OGS President for his consulting in the development of this supplement as well as his input in planning the meeting.

Thanks go to Jeffrey S. Eisenberg, managing editor of *Review of Optometry*, who distilled these complex lectures into the articles that follow, and to Martha Slawek, who handled the graphic design.

Finally, I would like to thank Pfizer, Inc. (Ravi Pherwani, Dennis Kowalski, Jill Burdge, Tom Wright, Karen Fixler), for their support of the OGS meeting and, in particular, for providing an unrestricted grant that allowed us to produce this supplement.

Please visit the OGS Web site, www.optometricglaucomasociety.org, and check out our quarterly e-journal that can be sent to your e-mail account free of charge. I hope you enjoy this supplement and find it useful.

Murray Fingeret, OD
Executive Vice-President, Optometric Glaucoma Society
Editor, Proceedings of the Seventh Annual Scientific Meeting of the Optometric Glaucoma Society

OGS Ezell Fellow Presentation

Retinal Nerve Fiber Layer Thickness In Experimental Glaucoma: Comparison Of OCT and Confocal Microscopy and Analysis Of Neural and Non-Neural Composition

BY JOE WHEAT, OD

Optical coherence tomography (OCT) is commonly used to image the retinal nerve fiber layer (RNFL) in glaucoma, but studies comparing RNFL thickness measurements from OCT and actual histological measurements are limited. Furthermore, it has been noted histologically that there is an increase in glial content in the RNFL of eyes with glaucoma, which may confound the interpretation of OCT measurements. The purpose of the present study was to compare OCT and histological measurements of RNFL thickness and to quantify the non-neural and neural content in these regions for glaucomatous and non-glaucomatous eyes in experimental glaucoma.

Four sets of eyes from macaque monkeys, each with unilaterally induced glaucoma, were evaluated with confocal imaging. The circumpapillary area of the retina was stained with Alexa Fluro 488 phalloidin and DAPI and mounted. Confocal microscopy was used to capture sequences containing the entire thickness of the RNFL in various locations corresponding to areas measured with the OCT. A MATLAB program was developed to obtain measurements of the RNFL and is currently being modified to separate neural from non-neural components in the confocal images.

Results from two sets of eyes show relative agreement in thickness values derived from OCT and those obtained from the confocal images for both glaucomatous and control eyes (an average difference of 9.7˙µm ±14.1µm). Preliminary data evaluating content of neural vs. non-neural components in the RNFL show a relative increase in non-neural content in glaucomatous retina.

Based on the preliminary data, OCT measures correspond well with histological measurements performed with confocal imaging. Eyes with experimental glaucoma show a relative increase in non-neural components in the RNFL in addition to an overall decrease in RNFL thickness.

DR. WHEAT IS A CANDIDATE FOR A PhD IN PHYSIOLOGICAL OPTICS AT THE UNIVERSITY OF HOUSTON COLLEGE OF OPTOMETRY. HE IS THE FIRST OGS EZELL FELLOWSHIP RECIPIENT. THIS PAPER WAS CO-AUTHORED BY LOUVENIA CARTER-DAWSON, PhD; AND RONALD HARWERTH, OD, PhD. SUPPORTED BY NEI GRANTS R01 EY01139, P30 EY07751, AND T32 EY07024.

OGS Member Presentation

Anterior Segment Biomechanical Differences Between Ocular Hypertension and Glaucoma

BY MICHAEL SULLIVAN-MEE, OD

The purpose of this study was to determine which clinically measurable anterior segment biomechanical properties best differentiate ocular hypertension (OH) from primary open-angle glaucoma (POAG), and whether these variables are related to severity of glaucomatous visual field loss.

Subjects that were included in this study were prospectively recruited to participate in a longitudinal study investigating temporal relationships between intraocular pressure (IOP), clinical biomechanical properties, and the development/progression of POAG. This cross-sectional report utilizes the first-visit data for all participants with diagnoses of OH and POAG. Study data was obtained for each eye using the Ocular Response Analyzer (ORA), Pascal Dynamic Contour Tonometer (DCT), Goldmann applanation tonometer (GAT), Schiotz tonometer (cornea and sclera readings), ultrasound pachymeter, and standard automated perimeter (24-2 pattern, Sita-Standard, Humphrey VFA.)

One-way analysis of variance, unpaired t-tests and generalized estimating equations were used to compare OH and POAG groups. Correlational and linear regression analyses were completed to evaluate relationships between biomechanical factors and severity of visual field loss.

Fifty-seven eyes of 28 OH subjects and 69 eyes of 35 POAG subjects were studied. After adjusting for level of IOP and intra-individual correlations between eyes, multivariate analysis identified older age, larger differences between the two ORA-IOP parameters (corneal-compensated IOP [IOPcc] and Goldmann-correlated IOP [IOPg]), and larger differences between DCT-IOP and GAT-IOP as independent discriminators between POAG and OH. When the two IOP-difference parameters were omitted from the model, corneal hysteresis (CH) and age were identified with generally equal statistical strengths. Severity of visual field loss was best associated with age, the difference between IOPcc and IOPg, and the averaged value of CH and corneal resistance factor.

Clinically measurable anterior biomechanical properties may have value for glaucoma prognostication, with potentially greater utility than central corneal thickness alone.

DR. SULLIVAN-MEE IS THE DIRECTOR OF OPTOMETRIC EDUCATION AT THE ALBUQUERQUE VA MEDICAL CENTER. HE HAS PUBLISHED AND LECTURED EXTENSIVELY ON THIS TOPIC AND TONOMETRY. THIS PAPER IS COAUTHORED BY KATHY HALVERSON, OD; DENISE PENSYL, OD; GRETCHEN GERHARDT, OD; AND RON SCHRADER, PhD.

Undetected Eye Disease in Latinos: An Epidemic in the Making?

BY ROHIT VARMA, MD, MPH

Latinos are the largest minority group and the fastest growing segment of the U.S. population. Census 2000 data show that 35 million U.S. residents, or 12.5% of the population, are Latino. That number is expected to increase to 61.4 million by the year 2025.

Even so, there is little population-based data about blindness and visual impairment in Latinos. What we do know: Latinos also are the youngest ethnic group in the United States, with a median age of 25 years, and we can expect to see a significant increase in eye disease as this population ages.

With support from the National Eye Institute, in 1999, my colleagues and I launched the Los Angeles Latino Eye Study (LALES) to determine the burden of eye disease among Latinos age 40 and older, as well as the causes of blindness and visual impairment in Latinos; evaluate the impact of eye disease on the quality of life; and assess the use of health-care and eye-care services by Latinos.

We went door to door in six contiguous census tracts in La Puente (Los

Angeles County) to recruit subjects. To be eligible, subjects had to self-identify as Latino/Hispanic, and had to be age 40 or older on the day of the household screening.

We examined 6,357 Latinos, about 82%, of eligible subjects. Two-thirds of subjects were age 60 years and younger, 40% were male, and 63% were born in Mexico. (Other members of this ethnic group include patients from Cuba and Central America.) Two-thirds spoke English and Spanish, and two-thirds did not complete high school. We set up a community-based clinic and arranged for them to receive in-depth eye exams.

Undetected Eye Disease

Some 90% of eye disease among patients studied was undetected. The prevalence of eye disease is expected to rise tremendously either because of the aging population or because they are undetected due to lack of care. Factors associated with undetected eye disease include having a history of diabetes, older age, being uninsured, males, having less than high school education, low acculturation, two or more systemic comorbidities, and trouble getting eyeglasses.

The overall prevalence for visual impairment (<20/40 best-corrected visual acuity in the better eye) was 3% in the Latino population studied.[1] The overall prevalence for blindness (<20/200 best-corrected visual acuity in the better eye) ranged from 0.4% (ages 40 to 49) to 4.2% (older than 80). Older participants were more likely to be blind. No gender differences were noted. The percentage of Latinos with visual impairment since 2000 is projected to increase 73% by 2010, 200% by 2020 and 323% 2030. The number of Latinos with visual impairment is expected to increase from an estimated 500,000 in 2010 to 2.5 million in 2050.

Risk factors associated with visual impairment included female gender, history of ocular disease, unemployment, diabetes, marital status (separated/divorced or widowed), less than 12 years of education and age. Latinos 60 and older have one of the highest rates of visual impairment compared to blacks and whites in the United States.

Open-Angle Glaucoma

Nearly 5% of the Latinos studied had open-angle glaucoma. This prevalence increased with age, from about 8% for those in their 60s to 15% for those in their 70s. This is higher than the rate reported for whites and similar to that for blacks in the United States. The number of Latinos with glaucoma since 2000 is projected to increase 66% by 2010, 184% by 2020 and 280% by 2030.

Nearly 4% of Latinos had ocular hypertension, a risk factor for glaucoma. Major factors associated with elevated IOP include higher systolic blood pressure, greater central corneal thickness and having type 2 diabetes mellitus.[2] Other variables related to higher IOP included older age, female gender, higher diastolic blood pressure, larger body mass index, darker-colored irides, and having nuclear sclerosis.

Some 75% of Latinos whom we diagnosed with glaucoma or ocular hypertension were undiagnosed before participating in LALES. Also, subjects who had glaucoma but whose IOP was less than <21mm Hg were three times more likely to be undetected than those who had higher IOP. This finding suggests the need to discount the value of high IOP in screening for and diagnosis of glaucoma.

What Can Be Done?

Given that Latinos, one of the fastest growing segments of the population, have high rates of visual impairment and open-angle glaucoma, and that much of it is undetected, we need to pay special attention to this group. This means:

- Implementing screening and treatment programs for the Latino population, especially aging members.
- Providing health insurance.
- Better educating Latinos and other health-care professionals about the importance of eye care, especially in this population.

We owe it to these patients to try to lower the burden of undetected eye disease in the population at large and in this particular ethnic group.

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Changing Medical Care and the Impact On the Glaucoma Patient

BY SCOTT R. CHRISTENSEN, BA, MBA

An epidemic of glaucoma is on the horizon. Indeed, 67 million people worldwide, including more than 3 million in the United States, have glaucoma. Nearly half these people are unaware they have the disease. Glaucoma affects people of all ages, especially the aging baby boomers, and races.

Meanwhile, the health-care climate has changed. Patients want, need and demand more information about their illness, treatments, prognosis and available resources. However, health-care providers are often overworked, with too many patients and too little time. So, the needs of glaucoma patients often go unmet.

Outside Organizations

A successful outcome is more likely with additional support from doctors, family members, friends and fellow patients. And, the assistance and support from outside entities is warranted. These include:

- ***The Glaucoma Foundation***, which was started by Robert Ritch, MD, FACS, FRCOpth, in 1984 and supported by volunteers in various capacities. The foundation has provided some $4 million in research grants during the past decade. It also offers educational outreach and patient support, and hosts an annual think-tank made up of individuals from academia and corporate America.
- ***The World Glaucoma Organization (WGA)***, an independent global organization founded in 2002. Its mission is to optimize the quality of glaucoma science and care through communication and cooperation among international glaucoma societies, with glaucoma industries, glaucoma patient organizations and all others in the glaucoma community.

• ***World Glaucoma Patient Organization (WGPA)***, an affiliate of the WGA that was founded in 2004. Its purpose is to better the lives of glaucoma patients by encouraging the establishment of and cooperation among glaucoma patient organizations worldwide.

World Glaucoma Day

Concerned about the number of people who already have glaucoma and the number who could go blind, the WGA and WGPA sponsored the first World Glaucoma Day on March 6, 2008. The event was supported by the Glaucoma Foundation, the medical community and the pharmaceutical industry.

The purpose of World Glaucoma Day is to spearhead awareness activities and progressively increase understanding about glaucoma worldwide. More than 1,000 events—including symposia, conferences, walks, parades, screenings and literature dissemination—took place in more than 60 countries. A Web site (www.wgday.net) was launched.

The World Glaucoma Day concept was well-accepted globally, and doctors said it improved educational efforts for their patients.

Glaucoma Patient Organizations

Glaucoma patient organizations (GPOs) are often an extremely meaningful piece of a patient's program of care. They provide a wide variety of support for all parties involved in the patient's recovery program.

These groups are generally voluntary nonprofit organizations and are run by members for members. Membership typically is comprised of newcomers and more experienced patients to provide balance. They have minimal finances, which are funded by dues, membership fees and/or donations.

GPOs can be an important part of a patient's overall health improvement and treatment plan. They typically are led by sensitive and caring leaders who can help offer comfort and foster sense of self esteem and courage for the difficulties that lie ahead.

Sometimes they lobby and advocate on behalf of members. Meeting places typically include community health centers, local hospitals, churches and town meeting halls. They often have speakers, workshops, refreshments and time for socializing. Family members and friends are generally welcome as well.

Other GPOs meet online. These groups usually offer news information, research updates, online counseling, chat rooms, e-mail bulletins and links to other resources. Web-based GPOs are particularly useful for those who live in remote or rural areas, those who are unable to physically travel and people who prefer anonymity.

GPOs do not offer sure cures or speedy solutions. They are not forums for patients to reveal private or sensitive information or gripe sessions. And, they are not appropriate for everyone.

The landscape of health care has been altered forever. Patients have assumed a greater role in their own care, which is a positive development, but it puts a greater strain on medical professionals. Assistance and support from outside entities is warranted, necessary and welcome.

MR. CHRISTENSEN IS PRESIDENT AND CEO OF THE GLAUCOMA FOUNDATION, NEW YORK; PRESIDENT OF THE WORLD GLAUCOMA PATIENT ASSOCIATION, AMSTERDAM, THE NETHERLANDS; AND PRESIDENT OF THE ASSOCIATION OF INTERNATIONAL GLAUCOMA PATIENT ORGANIZATIONS.

Physician-Patient Communication And Understanding

BY ROBERT RITCH, MD, FACS, FRCOphth

Although we like to think that our glaucoma patients follow our instructions, many of us tend to underestimate how many fail to comply. Studies have shown that patients with chronic medical conditions take only between 30% and 70% of prescribed medication doses, and 30% to 50% discontinue therapy within one year.[1]

Even so, we cannot always detect poor compliance. In fact, patients with chronic diseases often improve compliance close to the next scheduled visit and taper off again afterward. Although clinical findings at that visit may reflect this recent compliance, a general deterioration of the patient's condition may be a sign of intervening periods of noncompliance.

The implications are significant. Patients who go blind are at increased risk of divorce, suicide and depression.[2,3] So, communication is especially important with glaucoma patients to prevent vision loss and, if vision loss occurs, help the patient cope.

Reasons for Noncompliance

The term "compliance" describes the extent to which the patient's behavior coincides with your recommendations. By contrast, "noncompliance" is failure—intentional or accidental—to comply with directions in the self-administration of any treatment.

Noncompliance is often associated with a lack of understanding about glaucoma itself and the treatment goals. Noncompliance increases the risk of disease progression and vision loss. Other reasons for noncompliance include: fewer resources (financial, support), the cost of replacement medications (as well as problems with insurance coverage), traveling or being away from home, and less availability and a less-than-supportive attitude of the doctor.

Another problem involves dyscompliance. In this instance, patients don't follow their regimens due to physical problems. For example, the patient may have trouble breaking the seal on the medication bottle, opening the bottle, tilting back his or her head, raising an arm above shoulder height and holding the bottle steady.

Tools of the Trade

There are several ways to improve compliance. Discuss the risks and benefits of treatment. Minimize the number of drugs and frequency of instillation. Also, make sure the patient understands the condition and importance of compliance.

In my practice, we use the following tools to educate patients:

• ***Handouts and reprints***. We have more than 40 different handouts, plus article reprints that discuss such conditions as angle-closure glaucoma, exfoliation syndrome, and pigment dispersion syndrome, as well as the use of complementary and alternative medicine.

• ***Instruction sheets***. Our instruction sheets discuss individual medications and regimens, proper instillation of eye drops, treatment of blepharitis and dry eye (a finding we've often observed in our glaucoma patients), and tapering of steroids in post-op patients.

• ***Video***. An educational video tells patients how they can keep their glaucoma under control and includes a demonstration of how to instill drops. One such video is available on YouTube at http://pl.youtube.com/watch?v=FhkRAalbluE.

Besides these tools, make sure the patient has realistic expectations. Also encourage him or her join support groups that increase their awareness of glaucoma.

Dealing with Depression

If, despite your best efforts, your patient suffers vision loss, be aware of the possibility of depression. Depression is partly related to degree of visual impairment, but it is more related to loss of ability to enjoy activities.

Also, depression causes added impairment, including listlessness and lack of motivation, interest, energy and initiative. These lead to even less activity for the patient, resulting in less enjoyment and worsening depression. (Realize that depression is especially severe early on.) And, depressed patients cannot do the work required to adjust to visual impairment.

A person who accepts this loss is better able to move forward and create a new positive identity. The sooner the patient begins work on adaptation, the better. Acceptance of blind identity and learning of new skills is critical for the ability to enjoy activities.

Be sure to look for symptoms of depression. Also, be honest and don't give patient's false hope. If necessary, be prepared to refer the patient for counseling services.

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DR. RITCH IS THE SHELLEY AND STEVEN EINHORN DISTINGUISHED CHAIR AT THE NEW YORK EYE AND EAR INFIRMARY.

Relating Visual Field Change To Disability in Glaucoma

BY DAVID CRABB, PhD

Surprisingly, little is known about how visual field defects at different stages of glaucoma affect patients' abilities to perform everyday functions, such as reading, reaching items on a supermarket shelf, driving, and even walking without the risk of falling. For that reason, we have begun a series of lab-based studies that attempt to measure the (dis)abilities of glaucoma patients and relate them to each stage of the disease.

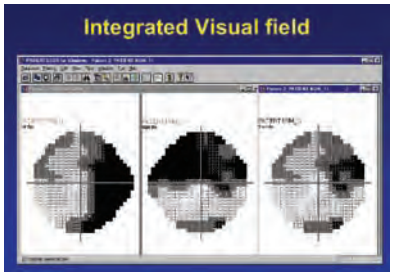
Eye-Hand Coordination

Do glaucoma patients have deficits in their ability to reach and grasp objects? To find out, we devised a lab based experiment using infrared reflective markers on the patients' hands, tracked by motion capture cameras as they reached and grasped household objects placed in different positions on a table in front of them.[1] We compared 16 bilateral glaucoma patients with 16 age-matched controls, measuring general kinematics (the speed of movement), reach dynamics and grasp dynamics.

The glaucoma patients exhibited a slower onset of movement as compared to control subjects. The patients had more difficulty in accurately reaching for an object, but no difference in grasp movements. This was explained by the patient's defects in their peripheral vision.

These abilities may partly depend on the location of the visual field defect. The glaucoma subjects with inferior field defects experienced more problems on this test than those with superior loss. These findings suggest that we should think carefully about the location of defects (inferior or superior) when managing patients and deciding to intensify treatment.

Fit to Drive?



For an integrated visual field, we overlay the right and left fields to generate a binocular representation by calculating the maximum sensitivity at each corresponding location.

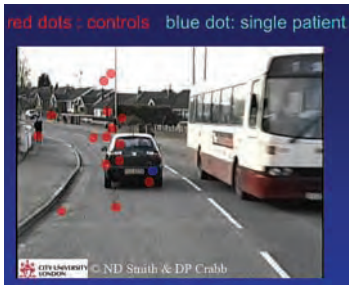
Binocular visual fields are better than monocular ones when assessing a glaucoma patient's fitness to drive, even though these are not routinely performed. In the United Kingdom, patients who have glaucomatous field defects in both eyes must, by law, undergo the binocular Esterman Visual Field test. However, the Esterman test is based on a grid that was developed more than 25 years ago and was not intended to measure visual fields as they relate to driving.

Our approach is to use an "integrated visual field." Using PROGRESSOR visual field software (Medisoft Ophthalmology), we overlay the right and left monocular fields to generate a binocular representation and calculate the maximum sensitivity at each location.[2,3] We found that there was close agreement between this technique and the Esterman.[4-6]

In some instances, when using other performance-based tests as an arbiter, the integrated visual field was a better predictor of the visual function needed for good driving performance than the Esterman. Also, no extra test time was required. So, at the very least, the integrated visual field may be an appropriate way of screening patients to determine whether further binocular testing is necessary.

Eye Movements

Eye movements are a neglected measurement in glaucoma. We wanted to determine whether they correlate to driving tasks and visual field defects. For this study, we employed the Hazard Perception Test (HPT), a PC-based test used to educate new drivers in the United Kingdom. Subjects



For this study, we employed the Hazard Perception Test. The dots represent points of regard for the subjects viewing the driving scene.

view on-road videos filmed from the driver's view and must detect hazards that would mean the camera car braking or taking evasive action. We planned to examine eye movements during the HPT to determine whether they differ in glaucoma patients and to relate visual field defects to the hazards.

Using head-mounted, state-of-the-art eye tracking equipment, we compared saccades, fixations and smooth pursuits between 15 patients with bilateral glaucoma with field defects in both eyes, and 25 age-matched control subjects. The glaucomatous patients made more saccades than the control subjects, but the saccades made by the control subjects were of larger amplitude.

Given this finding, we wondered if the glaucoma patients viewed a similar area as the control subjects or missed things that those control subjects saw. Using a quantitative eye movement measure known as the bivariate contour ellipse analysis, we determined that, on average, the glaucoma patients generally viewed the same area and picked up the same hazards, but had to make more saccades than the control subjects. However, looking at individual cases revealed the impact of peripheral visual field defect in detecting some hazards, such as pedestrians as they attempted to cross the road.

These results show that eye movements of glaucoma patients are different than those of age-matched controls. Furthermore, this type of research might lead to investigations that will provide better standards for the visual field required for fitness to drive.

Find an Object

In another recent lab-based study, we measured the ability of patients with bilateral glaucoma to locate an everyday scene pictured on a computer screen and compared the results to those from 16 aged-matched controls. We placed subjects 60cm from a 22-inch monitor, then recorded eye movements and the time required to locate an object. For example, participants were asked to find an item in picture of a supermarket shelf. The glaucoma patients took longer to locate the objects and their eye movement patterns differed from control subjects

Eye movement studies in glaucoma have received little attention, but they now might provide a "window" into the functional consequences of disease. More information about the studies conducted in our Measurement Techniques in Vision Laboratory can be found at: www.staff.city.ac.uk/d.crabb

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DR. CRABB IS A READER IN STATISTICS AND MEASUREMENT IN VISION AT THE DEPARTMENT OF OPTOMETRY AND VISION SCIENCE AT CITY UNIVERSITY IN LONDON. HIS RESEARCH FOCUSES ON CLINICAL MEASUREMENTS IN GLAUCOMA AND ALSO RELATING THESE TO VISUAL DISABILITY.

The OGS 2008 Honoree Lecture

Exfoliation Syndrome—Beyond the Eye

BY ROBERT RITCH, MD, FACS, FRCOphth

Exfoliation syndrome (XFS) is the most common identifiable cause of open-angle glaucoma (OAG), accounting for about 20% of cases worldwide. That translates into 60 million to 70 million individuals with XFS — not counting patients that have subclinical XFS. Prevalence increases with age, and there are racial and ethnic variations. Surprisingly, however, XFS has been largely under-recognized, under-diagnosed, and under-researched, even though it is potentially reversible.

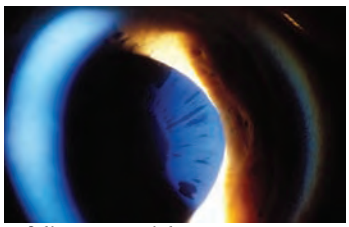
Exfoliation syndrome is an age-related generalized disorder of the extracellular matrix.[1] It is characterized by the production and progressive accumulation of a fibrillar extracellular material in many ocular tissues. It is a distinct disease, with specific mechanisms of development and distinct biochemical and cellular abnormalities. It is a protean disease, characterized by stress-induced elastosis due to excess production and abnormal aggregation of elastic fiber components.

Exfoliation material can be found in many organs, meaning that it may really be a systemic disorder, with glaucoma as an ocular manifestation. XFS is increasingly associated with cardiovascular and cerebrovascular disease. Exfoliation material is present in the walls of posterior ciliary arteries, vortex veins and central retinal vessels, and in autopsy specimens of heart, lung, liver, kidney, gallbladder and cerebral meninges.[2,3] Systemic associations include transient ischemic attacks (TIAs), stroke, hypertension, angina, myocardial infarction, Alzheimer's disease, hearing loss and hyperhomocysteinemia.

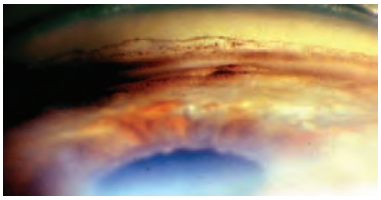
The exfoliation material in the eye is produced by the iris pigment epithelium, the ciliary epithelium and the lens epithelium, then deposited onto the lens. As the material thickens, the iris starts scraping it off the lens, scattering it over the anterior segment and depositing it in the trabecular meshwork. The trabecular cells also produce exfoliation material, suggesting a likely dysfunction in the trabecular cells as well.

The Glaucoma Connection

About one-fourth of individuals with XFS develop elevated IOP as the trabecular meshwork becomes blocked (most likely by a combination of pigment and exfoliative material), and about one-third of these patients develop glaucoma. The prognosis for XFS is worse than that of primary open-angle glaucoma in that patients with XFS have a greater mean IOP (IOP can reach the 50s and 60s) and a greater IOP fluctuation on diurnal exam compared to normal controls. The disc and visual field damage are typically worse on presentation.



Exfoliatve material as seen on the lens.



Angle pigmentation in exfoliative syndrome.

Patients who have XFS are more likely to convert from ocular hypertension to glaucoma. They have twice the risk of progression as patients with other forms of glaucoma, according to the Early Manifest Glaucoma Trial.[4] They also are more likely to require surgery and account for a greater proportion of blindness.

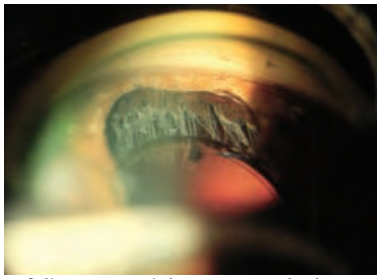
One question remains, however: Three out of four patients with exfoliation do not develop elevated IOP. So, what is the relationship between the mere presence of exfoliation material alone, elevated IOP and glaucoma? Is pigment necessary for the development of elevated IOP? Are there genetic factors or modulators involved? Future research will need to answer these questions.

A recent milestone study showed that two common single nucleotide polymorphisms are specifically associated with XFS and exfoliative glaucoma.[5] These are found in the coding region of the lysyl oxidase-like 1 (LOXL1) gene on chromosome 15. LOXL1 is a member of the lysyl oxidase family of enzymes, which are essential for the formation, stabilization, maintenance and remodeling of elastic fibers. These enzymes prevent age-related loss of elasticity of tissues.

LOXL1 protein is a major component of exfoliation deposits. When the polymorphisms are homozygous, they account for 99% of XFS. About 25% of the general population is homozygous for the highest-risk haplotype, and their risk of suffering from exfoliative glaucoma is more than 100 times that of individuals carrying only low-risk haplotypes.

Predisposing factors for XFS include weak zonules, lens thickening and forward movement, iris rigidity and a sluggish pupil. These factors all make the anterior chamber angle more shallow, putting patients at risk for angle closure. Other ocular associations include reduced aqueous ascorbate levels, a factor that predisposes patients to cataract. There's also evidence that oxidative stress, inflammation and ischemia are associated with XFS.

What does this mean in terms of therapy? Traditionally, our goal in glaucoma therapy is to lower IOP. But, if this is a disease that involves oxidative damage and inflammation, we need other treatments that are geared toward the mechanism of the disease, preventing glaucoma and inhibiting the development of exfoliation material. This may involve antioxidants and anti-inflammatory agents. Other possible treatments include miotics, such as pilocarpine 2%, to limit pupillary movement, and increase trabecular outflow. Argon laser trabeculoplasty followed by maintenance therapy with pilocarpine is another option.



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The 2008 OGS President's Lecture

Low Pressure Glaucoma: Update and a Neuroprotective Clinical Trial

BY THEODORE KRUPIN, MD

When German ophthalmologist Albrecht von Graefe first observed large, suspicious cupping in patients whose intraocular pressure (IOP) was normal, the ophthalmologic community was stunned—so stunned that, under peer pressure, Dr. von Graefe renounced his theory that patients could have glaucoma without elevated IOP. And, for many years thereafter, clinicians only diagnosed glaucoma when the IOP was higher than 21mm Hg.

Perhaps Dr. von Graefe yielded too soon. When the subsequent invention of the Schiotz tonometer offered reproducible IOP measurements, once again, patients were observed to have glaucomatous optic nerve damage without elevated IOP.

As the definition of glaucoma has evolved, elevated IOP is now considered a risk factor for the disease—not the disease itself. Today, we define glaucoma as "an optic neuropathy characterized by a specific pattern of optic nerve head and visual field damage which represents a final common pathway resulting from a number of different conditions that can affect the eye … most (but not all) of which can cause elevated IOP."[1]

The American Academy of Ophthalmology's *Preferred Practice Patterns* further define open-angle glaucoma as "a progressive, chronic optic neuropathy in adults where intraocular pressure (IOP) and other currently unknown factors contribute to damage and in which, in the absence of other identifiable causes, there is a characteristic acquired atrophy of the optic nerve and loss of retinal ganglion cells and their axons."[2] Once again, IOP is mentioned only as a risk factor rather than a characteristic of glaucoma.

Furthermore, while the goal of treatment is to lower IOP, the aim of treatment is to halt the degenerative process that manifests as optic nerve and visual field damage.

As Dr. von Graefe suspected, glaucomatous optic neuropathy is not always associated with elevated IOP. "Low-pressure glaucoma" (also called "normal-tension glaucoma") is a subgroup of open-angle glaucoma in which untreated IOP is always in the statistically normal range, defined as being less than 21mm Hg.[3] IOP-independent mechanisms may be the main, if not the sole, causes of the neuropathy.

Population-based studies demonstrate that low-pressure glaucoma represents 20% to 39% of patients with open-angle glaucoma in the United States. Examples include:

- ***The Beaver Dam Eye Study***, in which 2.1% of 4,926 subjects had open-angle glaucoma. Of them, 32% of patients had IOP <22mg Hg.[4]
- ***The Baltimore Eye Survey***, which consisted of more than 5,000 patients. Researchers diagnosed glaucoma based on an abnormal visual field and cupping. And, 24% of the patients at time of screening had IOP <21mm Hg.[5]
- ***The Early Manifest Glaucoma Trial***, in which baseline IOP was <21mm Hg in 54% of subjects in the treatment group and 50% of untreated patients in the control group.[6]

Neurodegenerative Disorder

When we discuss glaucoma today, we are talking about a progressive neurodegenerative disorder with the common pathway to the whole glaucomatous process being the death of the retinal ganglion cell (RGC).

A healthy RGC exists due to a balance between death and survival factors, and is functionally connected to a target in the brain. All individuals have an age-related decrease in RGCs, but this loss does not result in functional handicap. In glaucoma patients, however, the RGCs are exposed to an excess of death signals or a decrease in survival signals. This shifts the balance toward death of the RGCs and the start of the glaucomatous process.

Current glaucoma treatment is directed to lowering IOP using medical therapy (eye drops), laser treatment, and/or surgery, to a level that stops progressive optic nerve damage. The efficacy of lowering eye pressure in low-pressure glaucoma has been reported.[7]

Laboratory research has shown the potential ability to manage glaucoma not only by lowering eye pressure, but by aiming treatment modalities (i.e., neuronal protectants) directly at the optic nerve. Possible therapies may include agents able to increase or prolong the survival rate of injured retinal ganglion cells.[8]

Neuroprotection is a strategy directed at keeping the retinal ganglion cells alive and functionally connected to their targets in the brain. In glaucoma patients, this strategy is directed to retinal ganglion cells independent of IOP, blood flow, and other possible mechanisms. Although alpha-2 agonists, such as brimonidine, have neuroprotective properties in laboratory studies, randomized controlled clinical trials are required to demonstrate proof of neuroprotective activity, both in the central nervous system and in the eye.

LoGTS

Such proof may come from The Low Pressure Glaucoma Treatment Study (LoGTS). This four-year, multi-center, triple-masked study was designed to compare visual outcomes of 190 patients ages 30 and older who have low-pressure glaucoma. To qualify, patients had to have low-pressure glaucoma in at least one eye with untreated IOP of 21mm Hg or less, reproducible baseline visual field loss, normal-appearing angles and visual acuity of 20/40 or better.

Researchers randomized subjects to receive brimonidine tartrate, a highly selective alpha-2 adrenergic agonist with known neuroprotective effects, or timolol maleate, a nonselective alpha-adrenergic antagonist, without reported neuroprotective properties. The goal: Attempt to alter the course of low-pressure glaucoma, as measured by visual field progression. Since both agents are similar in their ability to lower IOP, any treatment benefit to eyes receiving brimonidine may provide evidence for an IOP-independent mechanism of action. Every four months, subjects underwent a full-threshold 24-2 visual field exam and optic disc evaluation.

Study design and baseline patient characteristics, plus the baseline relationship of visual field and IOP asymmetry, have been published.[9,10] At the onset of the study, 72% of patients had visual field damage in both eyes. Disc hemorrhage was present at baseline in 29 patients. Central corneal thickness (CCT) had a normal distribution (the average was 543µm), and did not account for false low-pressure readings. Also, study results show that IOP asymmetry is unrelated to VF asymmetry, suggesting an unclear pathogenic relationship between IOP and glaucomatous damage in eyes with LPG.

When managing glaucoma patients, we routinely set a target IOP—a measurement in the anterior segment of the eye—and determine the most effective way to achieve it (i.e., medications, laser treatments, surgery).

However, if we start thinking about glaucoma as a progressive neurodegenerative disorder, we must take a step back. Our target is located posteriorly, namely the retinal ganglion cell. And, we now have to think about treatments that work beyond lowering intraocular pressure.

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Rates of Visual Field Progression In Treated and Untreated Glaucoma

BY PAUL H. ARTES, PhD

A 46-year-old glaucoma patient initially presented 12 years ago with moderately advanced visual field damage, namely -6.2 decibels (dB) of loss, including loss in the paracentral area. Over the past 12 years, the mean change in visual field loss has been -0.60 dB per year. Another patient with glaucoma, 58 years old, initially presented with -12.6 dB of

field loss, but his visual field has progressed at a rate of -0.22 dB per year. Which patient has a greater chance of developing visual disability?

Although the first patient started out with less damage, his disease has progressed at a faster rate. So, he is at greater risk of becoming disabled—a finding that demonstrates the importance of measuring the rate of change for visual field loss.

Most clinical studies in glaucoma report on the incidence of change, namely the percentage of patients who meet change by a given amount. This is useful when comparing groups of patients, such as those who receive treatment vs. those who remain untreated.

In the exam room, however, it is the individual's rate of progression that is the most important measurement. This tells us the patient's likelihood of developing visual disability, which in turn guides our treatment decisions to lessen the risk.

Estimating the Rate

Information about rates of progression in glaucoma comes from three sources:

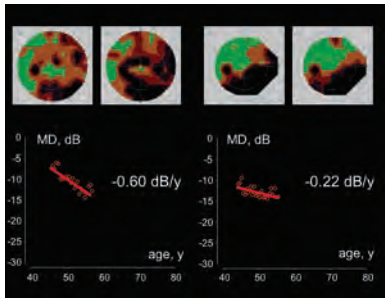
- ***For untreated patients, from cross-sectional data***. Using Goldmann visual field data from 151 patients who screened positive in the Baltimore Eye Survey, Harry Quigley, M.D., and colleagues estimated the average rate of change that the patients had been experiencing since developing glaucoma.[1] With some assumptions, their estimate translates to -0.40 dB to -0.90 dB per year. However, given the small sample size, this estimate was quite uncertain.

Dr. Quigley and colleagues updated their research last year, looking at 1,066 patients from nine population-based surveys of four ethnic groups using static perimetry.[2] The mean rates of change were highest among Chinese and Africans, at -1.56 dB/year and -1.33dB/year, respectively. Rates of changes were -1.12 dB/year for Europeans and -1.26 dB/year for Hispanics. An important finding was that in all ethnic groups, a few patients appeared to have progressed much faster than the majority.

- ***For untreated eyes, from longitudinal data***. In the Collaborative Normal Tension Glaucoma Study, 160 patients who had open-angle glaucoma (OAG) and IOP of less than 21 mmHg were followed without treatment for 3.8 years.[3] On average, patients progressed by -0.40 dB/year.

In the Early Manifest Glaucoma Trial, researchers randomized 126 patients with OAG to the untreated control arm and found an average rate of progression of -0.60 dB/year.[4] The Collaborative Normal Tension Glaucoma Study also showed that a few patients progress at a much more rapid rate than most others, but the distribution of rates of change in the EMGT has not yet been published.

- ***For treated eyes, from longitudinal data***. In the Halifax GL1 study, a prospective longitudinal study that was started in 1992, there were 102 patients with a mean age of 62 years at enrollment and a mean follow-up of eight years (four to 12 years). The mean change was -2.05 dB, for a mean rate of progression of -0.25 dB/year. Again, the most impressive feature of this data is the large spread in the rate of change. A large proportion of patients do not appear to change at all, while a few patients progress at an almost catastrophic rate.



Here are two examples of rate of visual field progression.

Systematic differences between these various studies are likely explained by different methodology and risk profiles of the patients enrolled. The important point, however, is that a few patients progress at much faster rates than the average. These few "rapid progressors" are at much greater risk of developing visual disability, and therefore they need to be identified early.

Putting It Into Practice

Now, how do we apply this in the exam room? A paper published last year offers some practical recommendations.[5] Two important considerations: What rates do we need to detect to prevent disability, and what rates of change can we expect to detect with current tools and frequent examinations?

Some suggestions: First, use perimetry frequently and consistently. Start with two fields at baseline, and then repeat the test every six months (or sooner). Use the same instrument and the same program, so that you can compare the data over time. Second, if there is sufficient data (say at least five tests), do the data justice. "Eye-balling" is unlikely to reveal everything that the visual fields can tell us. Use software, such as the Glaucoma Progression Analysis or Peridata.

A final suggestion: Even the best software cannot replace common sense and clinical judgment, particularly when it comes to the impact of visual loss on an individual patient.

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Structural and Functional Progression in Glaucoma

BY DAVID F. GARWAY-HEATH, MD, FRCOphth

Measuring progression is fundamental to managing glaucoma patients. This information helps us determine whether the patient's condition has worsened and, if it has, how quickly. It also helps us identify patients who may experience symptomatic vision loss during their lifetime and the efficacy of

treatment in slowing progression.

The identification of disease progression involves two measures: function, as measured by visual field testing, and structure, as measured by imaging. One problem often arises, however: In many clinical trials, some patients have measurable progressive changes at the optic nerve head, but no statistically significant changes in the visual field. In other patients, the opposite is true.

Published clinical trials offer several examples of this dissociation. Some examples:

- ***The Ocular Hypertension Treatment Society (OHTS)***, in which 4.2% of the patients progressed according to photos alone, and 2.7% progressed by visual fields alone. There was a small overlap of 0.7% of patients who progressed by both measurements.
- ***The Early Manifest Glaucoma Trial***, in which 45.9% progressed on fields alone, 0.4% progressed on photos alone, and there was an overlap of 7.1%.
- ***A study from Moorfields Eye Hospital***, in London, which followed 198 patients with ocular hypertension and 20 controls. Some 20.2% progressed by fields alone, 21.2% progressed by HRT alone and 12.1% progressed by both.[1]

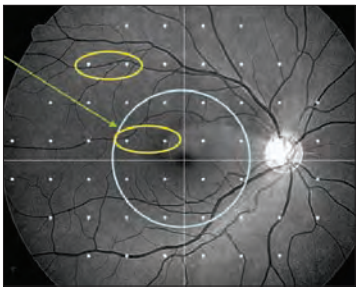
Given these findings, are structural and functional progression truly related? The short answer: "Yes." Individuals start off with a normal field and a normal disc, and at the end stage of glaucoma have a blind visual field and a very damaged disc.

There are various possible explanations for the apparent dissociation between structure and function measures of progression. These include test performance.[2] Imaging is less effective at measuring change when optic nerve head damage is advanced. Standard perimetry is less effective in patients in whom measurements vary greatly, or when learning effects might mask progression that's really occurring.

Additional explanations of why eyes are identified as progressing by structure or function, but not both, have to do with:

- ***Structural damage*** that is not directly related to loss of retinal ganglion cells. Examples include deformation of the lamina cribrosa, changes to pre-lamina tissue, and changes to the parapillary choroid and possibly the sclera.
- ***Functional loss*** that is unrelated to structural damage (e.g., ganglion cell dysfunction; media opacity).
- ***Measurement variability*** (poor signal-to-noise ratio) so that eyes that are truly progressing are missed. For example, in a modeling study, in which hypothetical patients underwent two visual fields per year for six years and had moderately variable fields, and when the progression criterion specificity was set to 95%, only 60% to 80% of truly progressing eyes were identified as progressing (depending on the analysis method used).[3]
- ***Different test criteria*** for specificity (or false positive rate) for progression. For the same group of subjects, if the test specificity is high, then the sensitivity (numbers identified as progressing) is lower. When the test specificity is low, then the sensitivity is higher. This is a difficult area, because there is no reference standard for progression, so researchers need to estimate the specificity of the 'progression criterion' from the clinical data.

The alternative is to assess the criterion in computer-generated models, where the 'real' progression rate can be specified and the specificity of a progression criterion tested directly. However, we cannot be certain that the models exactly reflect real clinical situations.



The central 20 degrees contains 50% of retinal ganglion cells, but only 12 out of the 52 test points in the Humphrey visual field. Thus, the visual field gives relatively greater emphasis to peripheral damage in glaucoma and will distort the structure/function relationship.

- ***Different measurement scales*** (linear for structure, logarithmic for function).
- ***Different anatomical sampling patterns.*** The visual field is centered on the fovea; structural measurements tend to be centered on the optic disc. It is possible that the sampling patterns influence our "model" of the way glaucoma evolves.

Not Linearly Related

There is considerable evidence that the relation between measures of structure and measures of function are not linearly related across the disease spectrum. This presents difficulties when comparing rates of change in structure and function at various stages of glaucoma damage, and may contribute to an apparent dissociation between structural and functional measurements of progression.

In early disease, and when both structure is measured in linear units and function in decibels, the structure appears to change more quickly than function (large changes in structure are associated with small changes in function). The opposite is true in more advanced disease.

The visual field is usually measured in a regular grid centered on the fovea, while measurements of the optic nerve head, or retinal nerve fiber anatomy, are usually measured centered on the optic nerve head. This different sampling of the anatomy of glaucoma damage also presents difficulty when comparing rates of change in structure and function because greater emphasis may be given to different anatomical regions by these sampling patterns. The dissociation does *not* necessarily imply that structure and function are *actually* changing at different rates.

New research is being undertaken to combine structural and function measurements to increase evidence that change has occurred (combining results reduces measurement variability) and to give more robust estimates of rates of change.

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Dissociation of Identified Structural and Functional Progression in Glaucoma

DAVID P. CRABB, PhD

The long-term aim of our research at City University London is to identify better ways to monitor disease progression in glaucoma. However, recent longitudinal studies indicate poor agreement exists between rates of glaucoma progression in terms of function (e.g., visual fields) and structure (e.g., scanning laser ophthalmoscopy) measurements currently used in the clinic.

In one study, researchers followed 84 patients with primary open-angle glaucoma for seven years using standard automated perimetry (SAP) and confocal scanning laser tomography (using the Heidelberg Retina Tomograph [HRT]).[1] With very specific statistical methods for detecting change they found no progression in 69% of subjects, 14% progressed by function alone, 13% by structure alone and only 4% by both function and structure.They concluded that "current clinical indicators of visual function (SAP) and measures of optic disc structure (HRT) provide largely independent measures of progression."

In another study, researchers followed 198 patients with ocular hypertension and 21 control subjects between 1994 and 2001 using SAP and HRT.[2] Seventy-three percent of patients showed no progression. Meanwhile, 15% progressed by function alone, 9% by structure alone and just 3% by both. "Agreement between optic disc progression and visual field progression is the exception rather than the rule," the authors concluded. Other studies present a similar picture.[3,4]

Measurement Noise

Do these studies mean that structural and functional progression in glaucoma patients occur independently from each other? This is unlikely. At City, we wanted to examine the hypothesis that this apparent disassociation between structural and functional measures is a result of measurement variability, or "noise," in the measurements we currently use. We examined this with a series of modeling experiments using "computer-generated" patients. Our model hypothesis: True underlying progression rates for both function and structure are identical. We started with a computer-simulated "patient" whom we assigned an identical rate of loss for both structure and function. The average rate of loss is set at 9% over three years, about a loss of 1 decibel per year for mean visual field defect. We then "add" varying levels of noise to the "patient's" measurements Results showed that:

- With low noise (related), 2% of patients experienced structural change alone, and another 2% of patients experienced functional change alone. There was a 73% overlap (patients who experienced both structural and functional change).
- With moderate noise (related), the rate for functional and structural change was 11% each, with a 32% overlap.
- With high noise (related), structural and functional change were 4% each, with 12% overlap.
- With high noise (independent), structure and functional change were 10% each, with 6% overlap.

So, the disassociation between the measures increases as the measurement noise gets worse, and when the variability is very high and independent (i.e., the level of noise is not related), the model mimics the results from published studies in real clinical data. From these findings, we conclude that measurement noise (variability) explains poor agreement between current tests in detecting structural and functional progression. Furthermore, the model suggests that measurement noise for visual fields is unrelated to that of structural measurements. So, a patient with highly variable images will not necessarily give highly variable field results and vice versa.

The statistical attributes of noise in imaging are generally neglected, but it might be important to characterize this to help with progression studies. For example, one of our Ph.D. candidates, Vicki Owen, has investigated the optimal frequency of imaging during follow-up to detect glaucoma progression by characterizing variability (noise) in neuroretinal rim area (RA), as measured by the HRT.[5] She found that noise was not normally distributed and was best characterized by hyperbolic distribution, which fit averages well while allowing for extreme values. Noise was greatly influenced by image quality, but age did not have a significant effect. Rates of detection improved with more frequent imaging, better quality images, and faster rates of disease progression.

Sensitivity of detection improves with more frequent testing, but if consistently poor-quality images are yielded for a patient, the probability of detection is low. Results from this work, and other studies in our laboratory in London, could be used to tailor individual follow-up patterns for patients with different rates of RA loss and image quality, especially in a clinical trial setting.

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Structural and Functional OCT in Glaucoma

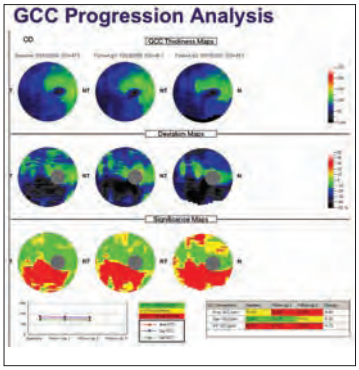
BY DAVID HUANG, MD, PhD

Traditional screening methods for glaucoma may not allow us to detect glaucoma at an earlier stage. As the Los Angeles Latino Eye Study pointed out, IOP is not a good screening criterion for glaucoma.

Visual fields also have become problematic, due to poor repeatability and reliability. For example, in the Ocular Hypertension Treatment Study (OHTS), 86% of abnormal and "reliable" fields were not confirmed on retest.[1] Three consecutive fields are required to reliably confirm conversion from ocular hypertension to glaucoma, according to OHTS. Even after three consecutive fields, however, some 12% of patients revert back to normal.[2]

Another consideration: Disc change precedes visual field loss in most cases. According to OHTS, without optic disc assessment, you might be missing 55% of cases in which there is disc change only.

But, optic disc assessment alone can be problematic as well. Optic disc



The RTVue FD-OCT system can map the macular ganglion cell complex (GCC), which consists of the axons (nerve fiber layer), cell bodies (ganglions cell layer) and dendrites (inner plexiform layer) of ganglion cells. The average GCC thickness can be measured precisely and followed over time to track glaucoma progression.

change using stereo disc photos is subjective and qualitative, with only moderate intra- and interobserver reproducibility.[3] Quantitative imaging—scanning laser polarimetry, scanning laser tomography and optical coherence tomography (OCT)—may detect glaucoma at an earlier stage and may improve the detection of glaucoma progression. I am a proponent of OCT.

OCT: The Next Generation

The newer generation, Fourier-domain (FD) OCT, offers several advantages than the standard time-domain (TD) OCT, especially in terms of speed. Consider:

- ***Traditional TD-OCT, when first introduced, was capable of capturing 100 axial scans per second.*** By 2002, TD-OCT was capable of capturing 400 axial scans per second. In 2006, the first FD-OCT retinal scanner, the RTVue, was introduced to the market place. The RTVue is capable of capturing 26,000 axial scans per second.
- ***FD-OCT can simultaneously acquire the 1,000+ pixels in an A-scans simultaneously, while TD-OCT only captures one pixel at a time.*** Therefore, FD-OCT can capture 20,000+ axial scans per second. The current generation of FD-OCT devices also offers improved axial resolution of 3µm to 8µm. Using the newer technology, details such as small blood vessels and photoreceptors (inner and outer segment) become clearly visible. By 2008, six other manufacturers have also introduced FD-OCT retinal scanners
- ***TD-OCT is susceptible to motion artifacts due to its slow capture speed.*** The faster capture speed of FD-OCT eliminates this motion artifact.

Diagnostic Accuracy

Glaucoma affects three areas in the posterior segment: the optic disc (cupping), peripapillary nerve fiber layer (thinning) and the ganglion cell (cell loss). Glaucoma also damages the ganglion cells in the macula, causing retinal thinning. The ganglion cell layer contains the cell bodies of the retinal nerve fibers, and in the macula, the ganglion cells take up greater volume than the nerve fibers. By concentrating on the ganglion cell complex (GCC) rather than the entire retinal thickness, we improve our ability to diagnose glaucoma.

Investigators have found that OCT-generated macular thickness maps offer less diagnostic power than measurement of circumpapillary nerve fiber layer thickness.[4-6] Also, retinal thickness mapping is not sensitive for detecting glaucoma because glaucoma preferentially affects the inner retinal layers. Diagnosis was improved by concentrating on the ganglion cell complex (the inner 3 retinal layers) rather than the entire retinal thickness.

FD-OCT provided greater diagnostic accuracy for assessment of macular ganglion cells. It also improved the repeatability of macular ganglion cell measurement and the potential to track glaucoma over time. High-speed mapping by FD-OCT improved the detection of nerve fiber layer loss in glaucoma as well as the repeatability of nerve fiber layer measurement and the potential to track glaucoma over time.

Blood Flow

Glaucoma also affects retinal blood flow, and poor perfusion to the optic nerve head and retina may be a risk factor for glaucoma progression. Current techniques (i.e., fluorescein angiography, ultrasound and Doppler flow meter) do not allow practical measurement of total retinal blood flow. OCT has been used to visualize, but not measure, total retinal blood flow.

We can compute flow in a vessel by measuring both Doppler shift and incidence angle. Flow direction relative to OCT beam is measured by 2 parallel cross-sections with total retinal blood flow measured by summing flow in all branch veins.[7]

The result of a pilot study was that glaucoma reduces retinal blood flow with visual field pattern standard deviation highly correlated with retinal blood flow.

Retinal blood flow measurement with Doppler OCT may help us understand the role of perfusion in the causation and treatment of glaucoma and other optic neuropathies.

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Recent Trends of Optical Coherence Tomography Imaging in Glaucoma

BY WOLFGANG DREXLER, PhD

Development of ultrabroad bandwidth light sources and high speed detection techniques have enabled a paradigm shift in ophthalmic optical coherence tomography (OCT) imaging performance, demonstrating the

potential of three-dimensional ultrahigh resolution OCT (UHR-OCT) at the cellular levels as well as depth resolved functional retinal imaging.

Most recent detector technology enables to perform more than 300,000 measurements/second, allowing 512 x 128 raster scans in 0.2 seconds ("snap-shot OCT"), more than one order of magnitude better than state of the art commercial technology. Isotropic sampling over 512 x 512 x 512 pixels with 600 frames/second is therefore possible in less than a second enabling higher clinical feasibility of 3D-OCT.

These developments lead to high definition visualization in stratified organs, providing more A-scans per B-scan and B-scans per volume. The end result is an optical analog to computed tomography (CT) or magnetic resonance imaging (MRI) over a smaller volume but on a microscopic resolution level and, while ophthalmologists might not yet have the time to look at and profit from all these data as a radiologist would, more precisely extracted thickness maps of several major intraretinal layers offer a wealth of information with huge diagnostic potential.

In addition to all the major layers of the retina, the entire choroid down to the lamina cribrosa and sclera can now be visualized. This enables unprecedented information about choroidal vasculature without any contrast agents, choroidal thickness and will enable quantification of choroidal blood flow in the near future.

The resolution advantage in conjunction with full volumetric sampling has led to the development of more informative quantitative indices of axonal damage and neuronal loss in glaucoma compared with measurements of retinal nerve fiber layer (RNFL) thickness and cup-to-disc ratio. One novel mapping method: the three-dimensional minimal distance mapping (3D-MDM) as the optical correlate of true retinal nerve fibre layer thickness around the optic nerve head region, therefore replacing the misleading projected thickness by its three-dimensional counterpart.

Quantification of three-dimensional surfaces leads to simple, automatically generated parameters for monitoring of disease progress that can be used to evaluate the individual situation. In a preliminary study, a significant relation between the cross-sectional areas of the retinal nerve fiber layer and the optic nerve was found to be a sensitive measure of axon loss.

Furthermore, UHR-OCT has the potential to image tissue *in vitro* with a resolution better than 2µm, allowing to detect the optical signature for apoptosis (cell death) of cultured retinal ganglion cells.

Additional Developments

The development of light sources emitting at alternative wavelengths, e.g. around 1060nm, enabled not only unprecedented three-dimensional OCT visualization of the entire choroid up to the choroid-sclera interface but also improved OCT performance in cataract patients due to less scattering losses in this wavelength region.

Adaptive optics using deformable mirror technology with unique high stroke to correct higher order ocular aberrations in combination with specially designed optics to compensate chromatic aberration of the human eye interfaced with three-dimensional UHR-OCT, recently enabled *in vivo* cellular resolution retinal imaging including visualization of photoreceptors as well as retinal pigment epithelial cells.

In addition, extensions of UHR OCT have been developed that enable non-invasive depth-resolved functional imaging of the retina, providing spectroscopic, blood flow or physiologic tissue information. These extensions of OCT should not only improve image contrast, but also should enable the differentiation of retinal pathologies via localized metabolic properties or functional state.

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New Targets for Optic Nerve Head OCT Imaging in Glaucoma

BY CLAUDE F. BURGOYNE, MD

The clinical detection of the onset and progression of glaucomatous optic neuropathy is essential to the care of every glaucoma patient. Although at present, optical coherence tomography (OCT) is principally used to measure retinal nerve fiber layer thickness, spectral domain OCT (SD-OCT) offers the opportunity to visualize, delineate and quantify the deep neural and connective tissues of the optic nerve head (ONH) and peripapillary sclera.

While the nerve fiber layer (NFL) surface is currently the anatomic source of the reference plane when performing OCT, we believe that in the future the reference plane for SD-OCT imaging will be based on Bruch's membrane. Such a reference plane should be more stable than the NFL surface through the course of the neuropathy. This development will better allow early glaucomatous thickening of the prelaminar neural tissues ("axonal unhappiness"), thickening of the lamina cribrosa itself and deformation of the laminar tissues to be detected. Beyond, these alterations in tissue thickness and position, OCT signal changes may also suggest axonal transport disruptions that precede frank architectural change.

The principal targets of deep ONH imaging are Bruch's membrane—deformity of the of the peripapillary sclera can be found by imaging Bruch's membrane—and its innermost ending, the neural canal opening. The passageway for the axons to pass through the eye wall (the neural canal) starts with the Bruch's membrane opening, then moves through the border tissues of Elschnig, the sclera and finally into the orbital optic nerve.

Important secondary structures for SD-OCT imaging are thus the border tissues of Elschnig (the Border Tissues), the neural canal wall, the anterior and posterior scleral canal openings, the anterior and posterior scleral surfaces, and the scleral flange.

Histomorphometric Reconstructing of the Optic Nerve Head Underlies our Current Studies Using SD-OCT

Using a technique known as histomorphometric reconstruction, we have published a series of four papers on 3-D reconstruction of the optic nerve head using high-resolution (1µm voxel) serial histologic section images. Histomorphometry is a histological technique, but instead of obtaining histologic sections, we image the embedded tissue surface block, stain it, take a high-resolution photograph and cut a 1.5µm section. We repeat this process until we've obtained 900 to 1,200 serial section images for each optic nerve head. We then stack these images and divide them into 40 radial sections to delineate the principal architecture. After we've

delineated the principal architecture, we're left with point clouds that we use to construct surfaces. From these surfaces we are able to describe and quantify the important architecture of that particular optic nerve head.

We are now using this technique to study eyes that have been imaged with Heidelberg Spectralis SD-OCT prior to being histomorphometrically reconstructed. To compare the histomorphometric reconstruction to what the clinician actually sees, we colocalize a clinical photograph of the reconstructed ONH to the central retinal vessels within the reconstruction. We then colocalize the photograph and the reconstruction to the SD-OCT volume obtained from 295 serial OCT B-scans.

We are on the verge of publishing a series of papers that compare the histology and SD-OCT-detected anatomy to what the clinician sees as the clinical disc margin. What this research shows is that SD-OCT imaging is detecting the important anatomy of the clinical disc margin and that it is greatly enhancing our understanding of this structure. In the future, we believe this anatomy will be central to the creation of a zero reference plane for all SD-OCT imaging and eventually will be used to most accurately estimate the true size of the disc.

Deep optic nerve head imaging that includes the neural canal opening, lamina cribrosa and peripapillary sclera may offer a dramatic improvement in the early detection of glaucomatous damage and eventually allow engineers to build a clinical science that will assess ONH susceptibility.

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About the Optometric Glaucoma Society

The Optometric Glaucoma Society (OGS) was formed seven years ago to promote excellence in the care of patients with glaucoma through professional education and scientific investigation. The major objectives are to promote education of the membership and other health-care providers related to all forms of glaucoma; promote the acquisition of new knowledge about glaucoma, in part through the development of clinical research within optometry that is related to glaucoma; facilitate the dissemination of information about glaucoma to health-care providers and the public and, establish collaborative relationships with other related organizations.

There are 77 members in the OGS, coming from several countries around the world. The OGS is equally divided between clinicians and scientists, with O.D.s, Ph.D.s and M.D.s making up our membership. The OGS is a member of the World Glaucoma Association (WGA) with seven members on the faculty of the 2007 World Glaucoma Congress.

Additional information including membership information and the application, may be found on the OGS Web site at www.optometricglaucomasociety.org.

The OGS is involved in several programs related to improving optometric glaucoma education. We publish a quarterly electronic journal that is free of charge and available to anyone who wishes to subscribe. Individuals may sign up at the OGS Web site. We also publish an annual glaucoma handbook that is a review of glaucoma diagnosis and management. This is also available for free and distributed to 35,000 optometrists. Also, the OGS holds a glaucoma residents program each fall in which one new resident from each school participates. And finally, the OGS in collaboration with the American Optometric Foundation is funding an Ezell Fellowship in Glaucoma, which is intended to enhance the opportunities for post-graduate optometric glaucoma research.

The group photograph from the 2008 Optometric Glaucoma Society Annual Meeting, Anaheim, Calif.


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