RESIDENT / FELLOW RESEARCH DAY

Department of Ophthalmology and Visual Sciences

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Roy J. and Lucille A. Carver College of Medicine

University of Iowa Hospitals & Clinics

Iowa City, Iowa

Braley Auditorium, 01136 Lower Level, Pomerantz Family Pavilion

Friday, April 21, 2017

UNIVERSITY OF IOWA HEALTH CARE

Department of Ophthalmology and Visual Sciences

RESIDENT/FELLOW RESEARCH DAY – 2017

DEPARTMENT OF OPHTHALMOLOGY AND VISUAL SCIENCES

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Michael G. Anderson, Ph.D.
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Patricia A. Kirby, M.D., FRCPath
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Stephen R. Russell, M.D.
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Mark E. Wilkinson, O.D.

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RESIDENT/FELLOW RESEARCH DAY - 2017

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CORNEA

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Harinderpal S. Chahal, M.D.

OCULAR PATHOLOGY

Maria A. Foley, M.D.

PEDIATRIC OPHTHALMOLOGY

Orwa J. Nasser, M.D., MPH

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Christine J. Clavell, M.D. (Medical Retina)
Sun Young “Sunny” Lee, M.D., Ph.D.
James J. Peairs, M.D.
Jessica S. Watson, M.D.

RESIDENT/FELLOW RESEARCH DAY - 2017

RESIDENTS

THIRD-YEAR RESIDENTS

Steven M. Christiansen, M.D.
William E. Flanary, M.D.
Jaclyn M. Haugsdal, M.D.
Lucas T. Lenci, M.D.
Prashant K. Parekh, MBA, M.D.

SECOND-YEAR RESIDENTS

Thomas J.E. Clark, M.D.
Lindsay K. McConnell, M.D.
Matthew A. Miller, M.D.
Lorraine A. Myers-Provencher, M.D.
Tyler B.S. Risma, M.D.

FIRST-YEAR RESIDENTS

Stephanie K. Lynch, M.D.
Spenser J. Morton, M.D.
Aaron M. Ricca, M.D.
Brittni A. Scruggs, M.D., Ph.D.
Daniel C. Terveen, M.D.

PRELIM RESIDENTS-INTERNAL MEDICINE

Matthew Benage, M.D.
Anthony T. Chung, M.D.
Austin R. Fox, M.D.
Benjamin J. Janson, M.D.
Heather A. Stiff, M.D.

RESIDENT / FELLOW RESEARCH DAY – 2017

GUEST FACULTY

Elias Traboulsi, M.D.

Elias Traboulsi, MD, is Head of the Department of Pediatric Ophthalmology and Director of the Center for Genetic Eye Diseases at Cleveland Clinic's Cole Eye Institute. He is Professor of Ophthalmology at the Cleveland Clinic Lerner College of Medicine of Case Western Reserve University and Director of the Ophthalmology Residency Program at Cleveland Clinic. He is also Chairman of the Department of Graduate Medical Education at Cleveland Clinic.

Dr. Traboulsi is the Executive Vice-President of the International Society for Genetic Eye Disease and Retinoblastoma and Editor-In-Chief of *Ophthalmic Genetics*. He also serves on the Editorial Board of the *American Journal of Ophthalmology*.

He is a frequent guest speaker at national and international meetings, and the author of more than 300 scientific articles and book chapters. His book on *Genetic Diseases of the Eye*, published by Oxford University Press in 1999, is one of the major references on this topic.

Dr. Traboulsi's clinical and research interests include the management and genetics of strabismus and congenital cataracts, and the nosology of ophthalmic and general medical genetic disorders and syndromes. He has a special interest in ocular developmental biology and ocular malformations, retinal dystrophies, childhood glaucoma and other common and rare ocular diseases of children.

Education and Training

- Pediatric Ophthalmology Fellowship - Children's Hospital National Medical Center
- Ophthalmology Residency - Georgetown University Hospital
- Ophthalmic Genetics Fellowship - Johns Hopkins University
- Ophthalmology Residency - American University of Beirut Medical Center

The University of Iowa
Department of Ophthalmology and Visual Sciences
Resident and Fellow Research Program
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OPHTHALMOLOGY RESIDENT/FELLOW RESEARCH DAY
SCHEDULE OF EVENTS

Friday, April 21, 8:00 AM – 3:15 PM

8:00 Continental Breakfast

8:30 Welcoming Statements

8:35 **Budd A. Tucker, Ph.D.**, Wynn Institute for Vision Research – Hot Research Topics

9:00 – 10:00 **Scientific Papers, Residents, Session I**
Braley Auditorium

9:00 **Aaron M. Ricca**, sponsors, Elliot H. Sohn, Michael D. Abràmoff 1
Night Driving Ability and Dark Adaptation in Age-Related Macular Degeneration

9:12 **Brittni A. Scruggs**, sponsors, Chunhua Jiao, Cathryn Cranston, Edwin M. Stone, Robert F. Mullins, Budd A. Tucker, Elliot H. Sohn 2
Optimizing Subretinal Injection Conditions for Retinal Gene and Stem Cell Therapy

9:24 **Daniel C. Terveen**, sponsors, Michelle R. Boyce, Jesse M. Vislisel, Kenneth M Goins, Mark A. Greiner 3
Refractive and Astigmatic Outcomes of Descemet Membrane Endothelial Keratoplasty (DMEK) at a Tertiary Referral Center

9:36 **Spenser J. Morton**, sponsor, Michael D. Wagoner 4
Prevalence and Severity of Evaporative Dry Eye Syndrome after Cataract Surgery

9:48 **Stephanie K. Lynch**, sponsors, Abhay Shah, James C. Folk, Xiaodong Wu, Michael D. Abràmoff 5
Catastrophic Failure in Image-Based Convolutional Neural Network Algorithms for Detecting Diabetic Retinopathy

10:00 – 10:30 **Morning Break**

10:30 – 11:30 **Scientific Papers, Resident/Fellow, Session II**
Braley Auditorium

10:30 **Tyler B. Risma**, sponsors, Tony Klauer, Erin M. Shriver, Scott A. Larson 6
Diplopia After Orbital Trauma: Predicting Need for Surgical Treatment

Paper 7 Withdrawn

OPHTHALMOLOGY RESIDENT/FELLOW RESEARCH DAY
SCHEDULE OF EVENTS

Friday, April 21, 8:00 AM – 3:15 PM

11:30 – 12:30 **Keynote Speaker**
Elias Traboulsi - Braley Auditorium

12:30-1:30 **Buffet Luncheon**
Melrose Conference Room 1 and 2

1:55 – 3:00 **Fellow Scientific Papers, Fellows, Session III**
Braley Auditorium

OPHTHALMOLOGY RESIDENT/FELLOW RESEARCH DAY
SCHEDULE OF EVENTS

Friday, April 21, 8:00 AM – 3:15 PM

2:45-3:00	**Faculty Meeting/Judging For Research Day Awards**

RESIDENT / FELLOW RESEARCH DAY – 2017

Morning Session – Paper 1

Night driving ability and dark adaptation in age-related macular degeneration (AMD)

Aaron M. Ricca, M.D.

Primary Supervisors: Elliott H. Sohn, M.D., Michael Abramoff Ph.D., M.D.

Background and Purpose: The purpose of this research study is to gain knowledge of driving abilities in patients with AMD by comparing night driving and dark adaptation. In AMD, rods develop deficits prior to cones and are more susceptible to loss in early disease. This increases over time, resulting in poor visual function after viewing a bright light source, which can be viewed as a form of transient "night-blindness." Functional testing in patients with AMD is still very much in its infancy. The primary functional tests that are just now being explored include steady state thresholds with flicker stimuli, photo-stress recovery, and dark adaptation. AMD is a clinical diagnosis and prior to the development of these tests, visual function in patients was not assessed beyond Snellen visual acuity testing. AMD patients have impairment in dark adaptation compared to age-matched controls, and there is published evidence that abnormal dark adaptation may be a prognostic factor for developing AMD. Night driving requires effective dark adaptation, and no comparison has been performed evaluating a patient's dark adaptation function with night driving proficiency.

Methods: Inclusion criteria for this prospective study include: age 50 to 99 years old; clinical diagnosis of AMD with visual acuity better than 20/40; possess an unrestricted driver's license and have driven within the last 6 months; pseudophakia; abnormal AdaptDx. Exclusion criteria include those with advanced AMD such as GA or history of CNV; phakia; presence or history of any disorder that caused visual field loss. Control subjects will be age-matched, pseudophakic, have no clinical diagnosis of AMD, visual acuity better than 20/40 and not have a disorder that has caused visual field loss. Subjects will have an initial baseline ophthalmologic exam as well as dark adaptation testing via AdaptDx at the time of recruitment. The driving session will use a custom-built National Advanced Driving Simulator (NADS) mini simulator (Mini-SIM) which recreates a safe and controlled driving experience with control of environmental factors such as traffic and glare from other vehicles. We will look at several outcome measures from the Mini-SIM, including glare recovery and ability to drive with constant glare. We will also assess contrast sensitivity.

Results: We anticipate to find that patients with a diagnosis of AMD will have a delayed photostress recovery time measureable with AdaptDx testing, and that this recovery time will correlate with the level of performance on the night driving simulator.

Conclusions: We hypothesize that even mild AMD can result in significant delays in photostress recovery time on AdaptDx testing that correlate to a measureable difference in night driving performance documented on the NADS Mini-SIM when compared against age-matched controls.

Morning Session – Paper 2

Optimizing Subretinal Injection Conditions for Retinal Gene and Stem Cell Therapy

Brittni A. Scruggs, M.D., Ph.D.

Primary Supervisors: Chunhua Jiao, M.D., Cathryn Cranston, M.S., Edwin M. Stone, M.D., Ph.D., Robert F. Mullins, Ph.D., Budd A. Tucker, Ph.D., Elliott H. Sohn,M.D.

Background and Purpose: There have been no studies to define the effects of transplantation conditions on the cell health or surgical outcomes when injecting cells into the subretinal space. It is unknown whether higher injection rates can cause retinal damage; it is also unclear whether blebs from larger injection cannulas can still result in retinal reattachment. We aimed to dissociate patient-derived 3-D neurospheres to fully characterize the cell population(s) prior to surgical transplantation; we then compared the effects of cannula gauge, temperature, storage time, and injection speed on induced pluripotent stem cells (iPSC)-derived retinal precursor cell viability. Ultimately, we sought to analyze outcomes from several key components of surgery, including retinal reattachment with variably sized needle-cannulas and effect of injection rate on retinal morphology.

Methods: Patient fibroblast-derived iPSC colonies were exposed to various media over a series of 60-150 days to produce eyecup-like structures. A dissociation protocol using papain was optimized for increased cell yield, and these isolated cells were evaluated using immunocytochemical analyses to detect cell surface markers. One million isolated retinal precursor cells were suspended and then injected through cannulas of different gauges (*e.g.,* 31G vs. 41G). The percent of live cells was determined using an MTS assay, a colorimetric quantification of viable cells. The storage temperature (*e.g.,* room temp vs. 0 degrees Celsius) and length of storage (*e.g.,* 1 hour vs. 2 hours) were also tested using the MTS assay. All conditions were tested in three independent experiments in triplicate using cells isolated from three patients.

Yucatan mini pigs underwent vitrectomy and subretinal injection of 300uL of iPSC-derived RPE/photoreceptor precursor cells or control buffers using a 31G or 41G polyamide cannula. Indirect ophthalmology was performed at sacrifice (POW1-POM3) to detect retinal reattachment and RPE changes. Morphology of eyes was assessed on H&E stained paraffin sections. Immunofluorescence staining with anti-RPE65 antibody was used to detect RPE changes in a subset of eyes with pseudo-GA. Additionally, cadaveric pig eyes underwent vitrectomy and subretinal injection of 300uL of buffer at 1.8mL/min or 0.18mL/min using an automated injector. Eyes were immediately fixed in 4% paraformaldehyde then embedded in paraffin for morphologic analysis.

Results: It was determined that iPSC-derived neurospheres could be dissociated to isolate retinal precursor cells, and cell viability was optimized using the papain/DNase enzyme solution. We have done extensive staining of the neurospheres and have data suggesting that these cells stain positive for PAX6, Sox2, OTX2, MITF, among other cell surface markers. Our results suggest that there was a significant ($p<0.01$) decrease in cell viability when using the 41G cannula (79.33+/-6.52%) compared to the 31G cannula (53.32+/-3.12%).

For the survival surgeries, 100% had spontaneous reattachment using both 31G (n=32 eyes) and 41G (n=32) cannulas. RPE changes or pseudo-GA was seen in 12/32 eyes with the 41G cannula and 22/32 eyes with the 31G cannula. Histologically, of 11 eyes with pseudo-GA seen on exam, RPE was relatively

intact but there was depigmentation of the apical villi in 6 eyes; loss of RPE65 expression was seen. Of cadaveric eyes injected at a speed of 1.8mL/min, there was significant loss of RPE cells in 5/6 eyes compared to 0/2 injected at 0.18mL/min ($p<0.05$).

Conclusions: Both 31G and 41G cannulas can be used to successfully administer subretinal injections that will spontaneously reattach without need for air-fluid exchange in pigs. Higher bleb injection speeds may result in RPE changes or pseudo-GA seen post-operatively on ophthalmoscopy that correlates to RPE depigmentation and loss of RPE65 expression.

Long-term goals of this project include using these cell preparation and surgical techniques for autologous transplantation of induced pluripotent stem cell-derived retinal precursor cells into the subretinal space of patients with retinal degenerative diseases.

RESIDENT / FELLOW RESEARCH DAY – 2017

Morning Session – Paper 3

Refractive and Astigmatic Outcomes of Descemet Membrane Endothelial Keratoplasty (DMEK) at a Tertiary Referral Center

Daniel C. Terveen, M.D.

Primary Supervisors: Michelle R. Boyce, M.D., Jesse M. Vislisel, M.D., Kenneth M. Goins, M.D., Mark A. Greiner, M.D.

Purpose: To determine the refractive and astigmatic outcomes of the DMEK procedure and evaluate what variables contribute to large refractive shifts.

Methods: IRB approval was obtained. We performed a retrospective chart review of consecutive DMEK cases performed at a tertiary referral center since 2012. The primary outcome measure was pre-operative to post-operative change in corneal astigmatism and axis. Secondary variables include: pre-operative to post-operative change in subjective MRx, Pentacam data (central pachymetry, corneal power, and magnitude and axis of front and back corneal astigmatism), BCVA, and severity of Fuchs endothelial dystrophy. Patients were grouped for analysis based on amount of total corneal astigmatism (<1D, 1D-2D, >2D) and axis of astigmatism (WTR, ATR, Oblique).

Results: A total of 404 DMEK procedures were identified. The patients were predominantly female (60%) and the mean age was 70 years. We anticipate the DMEK procedure will induce a minimal amount of with-the-rule astigmatism consistent with a temporal clear corneal incision and a mild hyperopic shift.

Conclusions: We hypothesize that there will be a minimal amount of change in astigmatism with the DMEK procedure and that the power and axis of astigmatism will remain stable following the procedure. There may be an association with amount of astigmatism change based on central corneal pachymetry at the time of surgery. Patients undergoing DMEK may be able to safely undergo concurrent correction of astigmatism.

RESIDENT / FELLOW RESEARCH DAY – 2017

Morning Session - Paper 4

Prevalence and Severity of Evaporative Dry Eye Syndrome after Cataract Surgery

Spenser J. Morton, M.D.

Primary Supervisor: Michael D. Wagoner, M.D.

Background: It is a common anecdotal observation that many patients with a history of cataract surgery have evaporative dry eye syndrome secondary to eyelid meibomian gland dysfunction. While the association between LASIK surgery and dry eye symptoms in young LASIK patients has been definitively documented, the association between cataract surgery and similar changes in older patients has not been conclusively determined. It is not clear whether the anecdotal observation of an increased prevalence of evaporative dry eye in eyes with cataract surgery is due to the coincidental occurrence of this relatively common condition in older patient populations or if the cataract surgery itself actually increases the likelihood of its development (when absent) or worsens its severity (when already present). Using the FDA approved LipiView imaging system, differences that exist, if any, between the prevalence and severity of evaporative dry eye syndrome in operated and non-operated eyes of veterans with unilateral cataract surgery can now be objectively and reproducibly identified.

Methods: We will prospectively perform evaporative dry eye evaluations on 100 consecutive veterans, aged 40 to 90 years, with a history of unilateral cataract surgery. The *inclusion criteria* for entry into the study includes: a history of unilateral cataract surgery with no other ocular previous ocular surgery and no other ocular comorbidity other than bilateral ocular hypertension with identical topical management, bilateral open angle glaucoma without surgical interventions and identical topical management, bilateral diabetic retinopathy without laser intervention, or bilateral macular degeneration without ocular injection therapy. The *exclusion criteria* includes: any previous ocular or eyelid surgery, any previous laser procedure (other than YAG capsulotomy), previous ocular surface infections or inflammation (other than those associated with dry eye syndrome), previous corneal inflammation or infections, or intraocular infections or inflammation. *Data* that will be collected includes LipiView imaging of the meibomian glands and tear lipid layer thickness, meibomian gland expressibility, tear film break up time, and fluorescein staining score. The *main outcome measure* will be differences that exist, if any, between the meibomian gland anatomy in the operated vs. non-operated eye. Differences between the right and left eye (definitely worse, probably worse, similar, probably better, definitely better) will be graded by 5 masked observers (who will not be informed the identity of the operative eye) at a single reading session after the enrollment is complete. *Secondary outcome measures* will be differences that exist, if any, between the operated and non-operated eye with respect to the thickness of the lipid tear film layer (mean, nadir, range), meibomian gland expressibility (measured on a scale of 0 to 15), tear film break up time (measured in seconds), and fluorescein staining (graded on a scale of 0 to 8).

Results: Patient recruitment was begun on March 22nd 2017. Several veterans have already enrolled in the study. Enrollment is expected to be complete by December 31st 2017. Preliminary data supports our hypothesis that more advanced meibomian gland abnormalities and evaporative dry eye syndrome are present in eyes with unilateral cataract surgery.

Conclusion: Our pilot study will offer the opportunity to objectively quantify the contribution of cataract surgery to the development of progressive meibomian gland dysfunction and its associated evaporative dry eye syndrome. We believe that we may be able to identify a statistically significant association between cataract surgery and the development of these adverse events from the initial cohort. If present, we hope to be able to identify sub-populations (age, surgical interval, need for YAG capsulotomy, different postoperative management, etc.) that are at increased risk for development of this complication, although it is very likely that expanded patient enrollment may be needed to establish statistical significance for specific risk factors. Our ultimate goal is to develop prophylactic strategies that will help reduce the prevalence and severity of cataract surgery-related dry eye syndrome.

Morning Session – Paper 5

Catastrophic Failure in Image-Based Convolutional Neural Network Algorithms for Detecting Diabetic Retinopathy

Stephanie K. Lynch, M.D.

Primary Supervisors: Abhay Shah, B.E.,[2] James C. Folk, M.D.,[1] Xiaodong Wu, Ph.D.,[2] Michael D. Abràmoff, M.D., Ph.D.,[1,2,3]

[1]Ophthalmology & Visual Sciences, University of Iowa Hospitals & Clinics, Iowa City, IA, United States.
[2]Electrical and Computer Engineering Department, University of Iowa, Iowa City, IA, United States.
[3]IDx LLC, Iowa City, IA, United States

Background and Purpose: Convolutional neural networks (CNNs) outperform retinal specialists in detecting diabetic retinopathy (DR). There are two principal CNN designs: 1) image-based deep learning algorithms, such as that developed by Google Inc.,[1] in which a CNN trains based on whole images, and 2) hybrid algorithms, in which multiple, semi-dependent CNNs train based on the appearance of focal lesions [2]. We compared the performance of these two CNN designs on adversarial (confounder) images, in which a small fraction of pixels have been modified.

Methods: Ten (10) DR images were selected from a reference set. The images were subjected to slight pixel modifications through a process called adversarialization. This was performed as follows: the 10 DR images were presented to an image-based CNN, which had already been trained on 500k DR images (AUC 0.9) to high performance. The diagnostic output for the 10 images was re-labeled from 'DR' to 'normal.' The resulting error was back-propagated into the image through 450 iterations; pixels in each image were updated iteratively at the input layer as $\varepsilon \text{sign}(\nabla x J(\theta,x,y))$, where ε is the small learning rate (0.001) and $\nabla x J(\theta,x,y)$ is the gradient of the Jacobian. Ten (10) adversarial images resulted. These were input into the hybrid algorithm, trained on a set of 5 million image components (AUC 0.98), to determine if DR would be detected.

Results: The difference between the adversarial images and the original DR images averaged 0.5-1.3 pixel values (0.12%-0.51%). Clinicians and the hybrid algorithm identified the adversarial images correctly as 'DR,' despite the fact that the image-based system classified all of them as normal.

Conclusions: Although both image-based and hybrid systems perform equivalently on validated datasets, image-based systems may fail catastrophically when confronted with adversarial images. They are sensitive to extremely small changes, potentially leading to false negatives. Hybrid algorithms based on multiple semi-dependent CNNs may offer a more robust option for clinical screening.

References

1. Gulshan V, et al. Development and validation of a deep learning algorithm for detection of diabetic retinopathy in retinal fundus photographs. JAMA. 2016 Dec 13;316(22):2402-2410.
2. Abràmoff MD, et al. Improved automated detection of diabetic retinopathy on a publicly available dataset through integration of deep learning. Invest Ophthalmol Vis Sci. 2016;57(13):5200-5206.

RESIDENT / FELLOW RESEARCH DAY – 2017

Afternoon Session – Paper 6

Diplopia After Orbital Trauma: Predicting Need for Surgical Treatment

Tyler B. Risma, M.D.

Primary Supervisors: Tony Klauer, C.O., Erin M. Shriver, M.D., Scott A. Larson, M.D.

Introduction: Diplopia after orbital trauma is a common problem encountered by eye care providers across multiple subspecialties. Strabismus after trauma can be self-limited but can also result in persistent strabismus by multiple mechanisms. This presents providers with the challenge of stratifying patients regarding their risk of needing strabismus surgery. There is little data describing which patients are most likely to go on to require strabismus surgery after orbital trauma. Additionally, all studies to date have been qualitative rather than quantitative when addressing ocular misalignment and type of surgery required in the setting of orbital trauma.

Methods: IRB approval was obtained and patients with ICD-9 coded visits for orbital trauma and diplopia seen at the University of Iowa between 1995 and 2015 were reviewed (N=404). Data from 265 patients were collected and included in this report.
Data collected from these charts included, demographics, radiologic characteristics, visual acuity, initial ocular misalignments in primary position and downgaze, final documented ocular misalignment in primary position and downgaze, dates and types of orbital and/or strabismus surgery.

Results: Patients were grouped based on whether they had no surgery, orbital surgery, or strabismus surgery. 45% underwent no surgery, 35% had orbital fracture repair alone, 6% had strabismus surgery alone, and 14% both orbital and strabismus surgery. Of the 96 (36%) had documented orthoptic measurements. Pearson correlation coefficients were calculated comparing the eventual need for strabismus surgery with several variables including age, gender, initial esotropia, initial exotropia, initial hypertropia, orbit fracture repair, and fracture location. There was a significant negative correlation between the presence of any initial esotropia and strabismus surgery, and a significant positive correlation between the presence of any exotropia and strabismus surgery.

Conclusions: Surprisingly, the presence of any initial esotropia was negatively correlated with the need for strabismus surgery; patients with any initial esotropia were 75% less likely to undergo strabismus surgery. Similarly, patients with any initial exotropia were more than three times as likely to undergo strabismus surgery. There were no other statistically significant correlations in demographics, fracture locations, or orthoptic measurements that were predictive of the need for strabismus surgery. It is difficult to explain the apparent protective benefit of esotropia against strabismus surgery or the positive correlation of exotropia with strabismus surgery. We recognize that given the relatively small number of patients undergoing strabismus surgery in this population, this result may change as more data are collected.

RESIDENT / FELLOW RESEARCH DAY – 2017

Afternoon Session - Paper 7

Fluorescein Angiography May Not Alter the Initial Management of Suspected Choroidal Neovascularization

Prashant K. Parekh, M.D., MBA.

Primary Supervisors: James C. Folk, M.D., Stephen R. Russell, M.D., Elliott H. Sohn, M.D., Michael D. Abràmoff, M.D., Ph.D.

Background: Fluorescein angiography (FA) has long been the standard modality to diagnose and manage choroidal neovascularization (CNV). However, FA is costly, has a mortality of 1 per 220000, and considerable morbidity from allergic reactions. Since the advent of anti-VEGF therapy for CNV, optical coherence tomography (OCT)--a non-invasive imaging method free of these disadvantages--is used extensively to manage CNV, while FA is primarily used to make the initial diagnosis. A recent study found the sensitivity and specificity of OCT compared to FA in diagnosis of CNV to be 100 and 80.8%, respectively. We hypothesize that FA changes the management of patients that are initially suspected of having CNV in less than 10% of cases. If this hypothesis is confirmed, it would cast doubt on the clinical utility as well as cost-effectiveness of FA for diagnosing CNV.

Methods: We retrospectively reviewed the FA, OCT, and clinical histories of 99 initial visits from 99 patients (99 eyes) who had an initial presentation of later-confirmed CNV. After de-identification, four retinal specialists masked to each other reviewed, in randomized order, the standard protocol: brief clinical history, posterior-pole color fundus image, and OCT scan of the initial visit. They then chose whether to manage each case by observation or three consecutive anti-VEGF injections (FA- arm). After re-randomization, corresponding early, mid, and late phase FA images were added to each patient's case data, and the experts again chose from these two management options (FA+). We determined for each expert, the case concordance (i.e., the percentage of cases where the management decision agreed between FA- and FA+) and inter-observer concordance (i.e., percentage of cases where all 4 experts agreed).

Results: Among our retina specialists, intra-observer concordances were 89.7%, 88.7%, 88.7%, and 95.9% (average 90.7%*, 95% CI* 83.7-97.6%). The average inter-observer concordance for the FA- arm was 83.8% (95% CI 72.1-95.5%) and the average inter-observer concordance for the FA+ arm was 81.8% (95% CI 68.5-95.2%).

Conclusion: Our data suggests a high degree of agreement in clinical decision-making whether or not FA was utilized. There was a similar level of agreement among specialists in the FA- and FA+ group, albeit at a higher variability. We believe these findings are reflective of nationwide, if not worldwide, practice patterns and further support deferring the use of FA for management of CNV, except in treatment failures and non-standard cases.

Afternoon Session - Paper 8

Visual Acuity at Different Thickness Levels of the Retinal Ganglion Cell Complex in Optic Neuropathies

Johanna M. Beebe, M.D.

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Introduction: Structure-function correlations with optical coherence tomography (OCT) have been made for patients with optic neuropathies, which relate retinal layer thickness to contrast sensitivity, color vision, and visual disability. We investigated the relationship between best corrected visual acuity (BCVA) and macular ganglion cell complex (GCC) or ganglion cell layer + inner plexiform layer thickness in ischemic optic neuropathy (ION), demyelinating optic neuritis (ON), and compressive optic neuropathy (CON).

Methods: Our institutions' electronic medical records was queried for patients between January 1, 2008 and August 3rd 2016 with a spectral domain Cirrus optic nerve OCT with GCC analysis. 719 patients were reviewed and patients with isolated ION, CON, or ON were identified. BCVA was recorded for each eye. OCT data was excluded if it was from the patient's acute presentation with associated optic nerve edema, and included if optic nerve pallor was note on exam.

Results: 54 patients with ION; 56 patients with CON; 15 with prior ON were identified. The 5th, median, and 95th percentile of BCVA (logMAR) were derived for several GCC layer thickness ranges: 40-49µm; 50-59µm; 60-69µm; 70-79µm; 80-89µm; for each type of optic neuropathy. The median and 95th percentile vision for the lowest GCC range was 20/63 and 20/20; 20/25 and 20/20; and 20/40 and 20/20 for ION, CON, and ON respectively. In 35 subjects who underwent measurement of visual fixation during OCT, mean GCC thickness in the region of fixation or in annuli centered at the fovea did not provide greater correlation with visual acuity than the global mean thickness.

Conclusions: The broad range of visual acuity possible in eyes at the lower range of GCC thickness argues for an adaptive gain control mechanism of cortical visual processing in some patients which, allows the maintenance of normal visual acuity in spite of a significant loss of retinal ganglion cells.

References: Sabadia S et al, 20/40 or Better Visual Acuity After Optic Neuritis: Not as Good as We Once Thought?, *J Neuroophthalmol.* 2016 Dec;36(4):369-376

Lee T, Ji Y, Park S, Heo H, Retinal ganglion cell and axonal loss in optic neuritis: risk factors and visual functions. *Eye*. 2016 Nov 18. doi: 10.1038/eye.2016.253

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Afternoon Session - Paper 9

Reduction of the Photopic Negative Response of Retinal Ganglion Cells in Optic Neuropathy: Assessment Using a New Portable Handheld Device

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Introduction: Our purpose was to evaluate the utility of a new handheld portable device to quickly ascertain the extent of optic nerve dysfunction by measuring light-evoked retinal ganglion cell function proximal to the site of optic nerve damage. Understanding the function of the retinal ganglion cells and metabolic coupling to blood flow may provide important prognostic information for recovery of vision. A portable device circumvents conventional requirements of foveal fixation, image clarity, an ERG laboratory, trained technician, and corneal electrodes.

Methods: A portable handheld ERG unit (RETeval/LKC) was used to record non-mydriatic photopic negative responses (PhNR) from surface eyelid electrodes. A miniature Ganzfeld stimulus provided 58 Td-sec red flashes, at 3.4 Hz, on a 380 Td blue background over 60 seconds under photopic conditions. 17 eyes with optic neuropathy due to ischemia, optic neuritis, or compression were compared to 31 normal eyes. The PhNR was assessed using four parameters (microvolts at 72 microseconds, P ratio, W ratio, and most negative amplitude). Retinal blood flow was assessed in each eye using laser speckle flowgraphy (Softcare Inc, Japan).

Results: There was a statistically significant decrease in the photopic negative response across all four parameters in eyes affected by optic neuropathy compared to normal control eyes, using unpaired non-parametric statistics (Mann-Whitney Rank Sum Test; p=0.002 for microvolts at 72 microseconds, p=0.001 for P ratio, p=0.014 for W ratio, and p=0.002 for most negative amplitude). Retinal blood flow was also significantly reduced in the eyes with optic neuropathy (p=0.001).

Conclusion: The PhNR measured with a portable, easy-to-use handheld instrument in a clinic exam room is a fast and effective way to assess retinal ganglion cell function proximal to the site of optic nerve injury. The PhNR and retinal blood flow may provide unique prognostic tools to assess potential for visual recovery.

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Afternoon Session – Paper 10

Imaging Vitreous Cell Using Optical Coherence Tomography

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Background and Purpose: Accurate measures of intra-ocular inflammation are critical for following disease severity and treatment response in uveitis. The International Uveitis Study Group reached consensus regarding a simple, standardized grading scheme for anterior chamber cell. However, grading vitreous cell remains a challenge. Vitreous haze grading is very subjective, and the group was unable to reach consensus regarding the classification of vitreous cell. Despite this, vitreous cell and haze are often included as primary endpoints for clinical trials in uveitis. A standardized, objective, and reproducible method for grading vitreous cell is needed for patients with intermediate, panuveitis, and posterior uveitis. Previous work has demonstrated that vitreous cells can be successfully imaged with spectral domain optical coherence tomography (OCT). However, a method of accurately grading vitreous cell using OCT has not yet been described. We aim to use Cirrus OCT to quantify the degree of vitreous cell in uveitis patients.

Methods: IRB approval was obtained. 28 eyes from 15 patients were imaged, including the uninvolved contralateral eye of 6 patients. OCT volume scans (512x128) of the posterior vitreous were obtained using the Cirrus 5000 HD-OCT (Carl Zeiss Meditec, Dublin, CA) by centering the scan on the fovea, with the retina at the lowest part of the scan window to maximize visualization of the vitreous. The clinical grading of vitreous cell in each eye, corneal and lens status, and diagnosis for each patient was recorded. The degree of cells from the OCT images was graded on a 0-2 scale for granularity and a 0-4 scale for clumped cells by a masked clinician.

Results: 21 eyes had active vitreous cell on clinical exam, 6 eyes were quiet (one eye was not clinically examined). Vitreous granularity was affected by media opacities and poor signal strength. The degree of clinical vitreous cell ranged from 0 to 2+ and the degree of clumped vitreous cell on OCT ranged from 0 to 3.5. The OCT grading of posterior vitreous cell and clinical grading of anterior vitreous cell appeared to differ in many instances.

Conclusions: OCT shows promise as a means of quantifying vitreous cell and monitoring the response to treatment in patients with ocular inflammation. Because granular signal on the OCT is affected by media opacity, the presence of clumped cells may be more clinically useful for OCT-based grading. The severity of these clumped cells on OCT does not appear to correlate well with clinical grading of anterior vitreous cell, but clinical grading is known to be highly subjective with low intra-grader reliability. Future studies involving automated grading of vitreous opacities on OCT may provide a way to quantify vitreous cell.

Afternoon Session – Paper 11

The Myocilin GLN368Stop Mutation in Normal Tension Glaucoma

Jason P. Kam, M.D.

Primary Supervisor: John H. Fingert, M.D., Ph.D.

Background/Purpose: Myocilin gene mutation can be found in up to 4.4% of primary open angle glaucoma patients. The GLN368Stop mutation is the most common molecular cause of myocilin gene mutation. We have found patients with GLN368Stop mutation in normal tension glaucoma. We investigated the role of the myocilin GLN368Stop mutation in normal tension glaucoma (i.e. primary open angle glaucoma that occurs at intraocular pressures < 22 mm Hg).

Methods: Cohorts of patients with normal tension glaucoma (n = 748) and unexamined control subjects (n = 1780) were tested for the most common myocilin mutation, GLN368Stop, which has been previously associated with glaucoma that occurs with high intraocular pressures (i.e. 30 mm Hg). The GLN368Stop mutation was assessed with either whole exome analyses or with quantitative real-time PCR. All positive results were confirmed with Sanger sequencing.

Results: Seven of 748 (0.94%) normal tension glaucoma patients and 7 of 1780 (0.39%) controls were found to have a GLN368Stop myocilin mutation. The GLN368Stop mutation was 2.4X more frequent in NTG patients than in control subjects, however, this difference was not statistically significant ($p > 0.05$).

Conclusions: Myocilin mutations have been previously associated with primary open angle glaucoma that occurs with high intraocular pressure. Our pilot study suggests that some cases of normal tension glaucoma may also be caused by myocilin mutations. A larger study with greater power will be necessary to determine if the GLN368Stop mutation is statistically associated with normal tension glaucoma.

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Afternoon Session – Paper 12

The Healing Process of Extra Ocular Muscles and Adnexa After Eye Muscle Surgery

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Primary Supervisor: Scott A. Larson M.D.

Background: Anterior segment ocular coherence tomography (AS-OCT) has been descried as a great modality to identify extraocular muscles. The AS-OCT provides good reliability and reproducibility, consistency and accuracy in measurement of the limbus-insertion distance. The ability to accurately image extraocular rectus muscle insertions using AS-OCT may have future implications for the preoperative procedure planning in patients who have had previous surgery. The healing process of ocular adnexa after extra ocular muscle surgery is not fully understood. AS-OCT can help in identifying anatomy and inflammatory activity after extra ocular muscle surgery, which is important in understanding the timing and pattern of healing process, like adnexal tissues edema resolution, muscle edema resolution, resorption of absorbable sutures and scars formation.

Purpose: To identify the healing patterns of extra ocular muscles and adnexa after eye muscle surgery.

Design and setting: This is a one site, IRB approved, prospective descriptive study.

Methods: Patients who are scheduled to undergo strabismus surgery and meet the inclusion criteria (age >18 years and < 80 years, able to perform regular post op follow up exams) will be asked to undergo serial AS-OCT imaging. AS-OCT will be performed using Cirrus machine preoperatively, 1 week, 4-6 weeks and 4-6 months' post operatively.

Descriptive analysis: Preoperatively; focus on identification of extraocular muscles and adnexa (conjunctiva, Tenon's membrane, rectus muscle and its tendon, location and thickness of muscle, muscle insertion location, sclera, pseudotendon/stretched scar). Postoperatively; focus on new anatomy and healing process (location of muscle compared to previous and planned location, amount and extension of edema/inflammatory reaction, blood pool and its resorption pattern (time and rate), sutures depth/location and their resorption pattern).

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Afternoon Session - Paper 13

Re-assessment: Does Herpes Zoster Cause Giant Cell Arteritis?

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Secondary Contributors: Erin M. Buckingham, Matthew J. Thurtell, MBBS, FRAP, Charles Grose, Randy H. Kardon, M.D., Ph.D.

Background: Giant cell arteritis (GCA) is a common form of vasculitis in people over the age of 65. Varicella zoster virus (VZV) is an exclusively human neurotrophic alpha-herpesvirus. It is the only human virus that has been shown to result in arteritis by replicating within arteries. Studies over the last 10 years have implicated VZV as the causative agent in GCA based on immunocytochemical identification of zoster antigens in temporal artery biopsies. Gilden *et al* found VZV antigen in 74% of 82 temporal artery biopsies obtained from GCA patients with positive temporal artery biopsies (Neurology 2015). The same authors have published several subsequent studies that identify VZV antigens in a large percentage of temporal artery biopsies from GCA patients. Another study by Pisapia and Lavi of 19 temporal artery biopsies failed to find VZV antigens in temporal artery biopsies (Exp Mol Pathol 2016). They concluded that all samples exhibited false-positive staining due to non-specific antibody binding.

Purpose: To evaluate temporal artery biopsies found to be positive for arteritis from patients with GCA for the presence of VZV antigens using both commercially available antibodies and highly sensitive non-commercial antibodies. Results will then be correlated light microscopic findings and clinical data.

Methods: Samples were selected from the files of the F.C. Blodi Eye Pathology Laboratory between 2015 to 2017. Samples from patients outside of UIHC were excluded. Each sample was then re-examined by an ophthalmic pathologist for histologic evidence of GCA. Only samples with convincing evidence of GCA were selected to study. Remaining unstained sections from these cases were assessed for the presence of zoster antigen by immunohistochemistry (IHC) and/or immunofluorescence.

Results: 16 GCA samples were analyzed, and categorized into likely positive for VZV, equivocal positive for VZV, and likely negative for VZV when compared with control tissues. Out of the 16 samples, 3 were likely positive for VZV (~19%), 3 equivocal and 9 negative. Positivity was found mainly in the adventitial layer of the artery.

Conclusion: Our study finds that the rate of positivity for VZV antigens in GCA-positive temporal artery biopsies is far lower than that found in previous studies. While the results obtained in different studies of VZV in GCA could have been affected by the sensitivity of antibodies used, the likely explanation for the high rate found in other studies is that lack of pathologic correlation lead to misinterpretation of false positive immunostaining as true positive staining.

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Afternoon Session – Paper 14

Fibrin Formation in DMEK Surgery

Michelle R. Boyce, M.D.

Primary Supervisors: Kenneth M. Goins, M.D., Mark A. Greiner, M.D

Background/Purpose: Descemet membrane endothelial keratoplasty (DMEK) is an effective procedure for the treatment of corneal edema due to poor endothelial cell function. Given the relatively recent introduction of DMEK, intraoperative occurrences such as fibrin formation have not been described sufficiently in the literature. Rapid formation of fibrin in the anterior chamber of the eye during the graft unfolding step can lead to difficultly with graft placement and prolonged graft opening and surgical times. The purpose of this study was to determine the incidence of fibrin formation during DMEK surgery, as well as associated donor and recipient characteristics.

Methods: A retrospective review was performed of eyes that underwent DMEK surgery at the University of Iowa between October 2012 and February 2017. The main outcome measures were intraoperative fibrin formation, and within this group, best-corrected visual acuity, surgical complications, graft unfolding time, endothelial cell density 6 months post-DMEK, use of anticoagulation at the time of surgery, and systemic inflammatory vascular diseases.

Results: A total of 360 DMEK surgeries were performed with 25 occurrences (6.9%, 23 patients) of intraoperative fibrin formation. Over a 6 month follow-up period, 22 cases had a best corrected visual acuity of 20/30 or better and 2 were 20/40. Repeat air injection was required in 6 cases (24%) and a second graft (DSAEK) was required in 3 cases. The average endothelial cell count at 6 months follow-up was 1553 cells/mm^2 (range 718-2052 cells/mm^2) for the 12 cases that data was available. The mean graft unfolding time was 20.5 minutes. Eighteen patients were taking anticoagulants at the time of surgery including 14 on aspirin, 3 on a nonsteroidal anti-inflammatory agent, and 1 on clopidogrel. Systemic inflammatory vascular disease was identified in the medical history of 14 patients including type 2 diabetes mellitus, cancer, and various autoimmune diseases.

Conclusions: Fibrin formation is a rare occurrence during DMEK surgery but is associated with prolonged graft unfolding times and higher than reported rates for the complications of re-bubble and endothelial cell loss. Visual outcomes remain excellent. Long term follow-up is needed to determine the effects on graft survival.

Afternoon Session – Paper 15

OCT - Neuroretinal and Outer Retinal Contributions to Visual Loss in Ocular Inflammatory Disease

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Primary Supervisors: James C. Folk, M.D., Michael D. Abràmoff, M.D., Ph.D.

Secondary Contributors: Zhihui Guo

Purpose: Patients with ocular inflammatory disease sometimes show progressive visual field loss. When we used our established algorithms to predict visual fields (Humphrey 24-2) from the neuro-retinal layers alone (which has been shown to have high correlation in neuropathies), correlation was unexpectedly low in these patients. The purpose of this study is to test the hypothesis that there is an outer retinal contribution to visual field loss in patients with ocular inflammatory disease.

Methods: 24 patients with idiopathic ocular inflammatory disease, confirmed by an uveitis expert and with known visual field defects on HVF 24-2, underwent pre-dilation standard Humphrey 24-2 SITA perimetry. After dilation, we performed our standard 9-field Spectralis OCT protocol, sequentially fixating on areas of retina 12.5° apart using a 3 × 3 grid pattern. This protocol entirely covers the 54° area tested with the HVF 24-2. Using our automated pre-trained machine learning OCT-PVTS algorithm, which achieves 0.74 correlation with HVF 24-2 in patients with glaucoma, each 9-field OCT was co-registered and the nerve fiber, ganglion cell, and inner plexiform layers were co-segmented and each of the 52 HVF 24-2 testpoint thresholds was predicted and compared to HVF 24-2 measured thresholds. In addition, we segmented the outer retina (from ONL to BM) in these same widefield OCT images. We compared the measured actual HVF 24-2 to the predicted HVF 24-2 (i.e. neuro-retinal analysis from widefield OCT) and to the outer retina thickness for each test location.

Results: Average correlation between actual and predicted HVF 24-2 thresholds was 0.53. The predicted visual field corresponded reasonably well in some subjects and not in other subjects. In these latter cases, measurement of outer retinal loss improved the correlation between the actual and predicted HVF 24-2 thresholds.

Conclusions: Automated prediction of visual field loss as seen on a HVF 24-2 from 9-field OCT may have a role in management of patients with ocular inflammatory disease, but may need to be combined with analysis of the outer retina. More importantly, simultaneous quantification of neuroretinal and outer retinal OCT shows that both are affected and contribute to visual function in these patients with Ocular Inflammatory Disease.

RESIDENT / FELLOW RESEARCH DAY – 2017

Residents and Fellows who have Completed Research Projects (Submitted and/or Published)

Stephen M. Christiansen, M.D. (PGY4)
Twitter at the 2014 and 2015 Annual Meetings of the American Academy of Ophthalmology 2016

Jaclyn M. Haugsdal, M.D. (PGY4)
Boston Type I Keratoprosthesis for Primary Congenital Glaucoma
British Journal of Ophthalmology 2016

William E. Flanary, M.D. (PGY4)
Cystoid Macular Edema after DMEK and Recent Versus Remote Cataract Surgery
Cornea 2016

Lucas T. Lenci, M.D. (PGY4)
Dermoid Cysts: Clinical Predictors of Complex Lesions and Surgical Complications
J AAPOS 2017

Prashant K. Parekh, M.D. (PGY4)
Fluorescein Angiography May Not Alter the Initial Management of Suspected Choroidal Neovascularizaton
JAMA Ophthalmology, submitted

Lindsay K. McConnell (PGY3)
An Analysis of Conjunctival Map Biopsies in Sebaceous Carcinoma
Ophthalmic Plastic Reconstructive Surgery 2017

Lorraine A. Provencher, M.D. (PGY3)
Investigating the Clinical Value of Urine Beta-2 Microglobulin in Patients with Tubulointerstitial Nephritis and Uveitis (TINU)
Ophthalmology, submitted

Thomas J. "T.J." Clark, M.D. (PGY3)
Hering's Law in Congenital Ptosis: Evaluation of the Contralateral Response to Unilateral Congenital Ptosis Repair

Matthew A. Miller, M.D. (PGY3)
Postoperative Hemorrhagic Occlusive Retinal Vasculitis Associated with Intracameral Vancomycin Prophylaxis during Cataract Surgery
Journal of Cataract and Refractive Surgery 2016

Jessica S. Watson, M.D. (Retina)
Breaking Bad: An Assessment of Ophthalmologist Interpersonal Skills and Training on Delivering Bad News
Ophthalmology, submitted

Harinderpal S. Chahal, M.D. (Oculoplastics)
Scleral Contact Lenses in an Academic Oculoplastics Clinic: Epidemiology and Emerging Considerations
Ophthalmic Plastic Reconstructive Surgery, submitted