RESEARCH DAY

Department of Ophthalmology and Visual Sciences
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

Saturday, April 26, 2014, 7:30 AM-3:40 PM
OPHTHALMOLOGY RESIDENT/FELLOW RESEARCH DAY
SCHEDULE OF EVENTS

Saturday, April 26, 2014, 7:30 – 3:40 PM

7:30 Coffee
8:00 Welcoming Statements

8:05 – 9:40 Scientific Papers, Residents

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<td>Scientific Papers, Fellows, Session I</td>
<td>Correlation of Decreased Contrast Sensitivity in Glaucoma Patients and Glaucoma Suspects to Ganglion Cell Layer Analysis on Cirrus OCT</td>
<td>Elisabeth F. P. Aponte, Chris A. Johnson</td>
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<td>David R. P. Almeida, James C. Folk and Stephen R. Russell</td>
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<td>John J. Chen, Randy Kardon; Michael Wall</td>
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<td>Oral Mineralocorticoid Antagonists for the Treatment of Central Serous Chorioretinopathy</td>
<td>Eric K. Chin, James C. Folk</td>
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<td>Cystoid Macular Edema and Glaucoma Filtration Surgery</td>
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<td>One Year Clinical Outcome of a Randomized Clinical Trial Investigating Pre-operative Adjunctive Bevacizumab for Tractional Retinal Detachment (TRD) Due to Proliferative Retinopathy (PDR)</td>
<td>Elizabeth O. Tegins, Elliott H. Sohn</td>
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<td>Lunch</td>
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OPHTHALMOLOGY RESIDENT/FELLOW RESEARCH DAY
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Saturday, April 26, 2014, 7:30 – 3:40 PM

1:30 – 2:20  Scientific Papers, Fellows, Session III
Braley Auditorium

1:30  Amanda C. Maltry, Supervisor, Nasreen A. Syed
Conjunctival Biopsy for Lichen Planus in Lacrimal Drainage Obstruction

1:40  Katrina Mears, Supervisor, Vinit B. Mahajan
Limbal-Trocar Cannulas for Complex Vitrectomy Surgery

1:50  Jordan J. Rixen, Supervisor, Mark A. Greiner
Diabetes Mellitus Increases Risk of Unsuccessful Graft Preparation in Descemet’s Membrane Endothelial Keratoplasty

2:00  Meredith A. Baker, Supervisor, Richard C. Allen
The Quantitated Internal Suture Browpexy or "Chicken" Brassiere Suture

2:10  John J. Brinkley, Supervisor, Randy H. Kardon
Neuro-ophthalmology Does Windows! Evaluation of Confocal Corneal Microscopy in Normal Subjects, Diabetes and Patient with Neurotrophic Cornea

2:20 – 3:10  Graduate Students / Post-doctoral Fellows
Braley Auditorium

2:20  Adam Hedberg-Buenz, Supervisor, Michael G. Anderson
Investigating the Influence of Blast on Cellularity in the Retinal Ganglion Cell Layer in a Mouse Model of Blast-induced Traumatic Brain Injury using a Semi-automatic Technique

2:30  Scott Whitmore, Supervisors, Robert F. Mullins and Todd E. Scheetz
Bioinformatic Analysis Uncovers Altered Gene Expression in a Cell Culture Model of Age-related Macular Degeneration

2:40  Mark Christopher, Supervisor, Michael D. Abramoff
Automatic Discovery of Optic Nerve Head Structural Features from Image and Genetic Data

2:50  Ralph Hazlewood, Supervisor, John H. Flugert, M.D.
Triplication of Upstream Regulatory Sequences Leads to Gene Dysregulation in Patients with Cavitary Optic Disc Anomaly

3:00  Dina Ahram, Supervisor, Markus H. Kuehn
A Canine Model of Primary Angle Closure Glaucoma Provides Insight into the Genetic Mechanisms of the Disease
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<td>Erin Burnight, Supervisor, Budd A. Tucker</td>
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<td>CEP290 Gene Addition Rescues Cilia Defect in CLA Patient Cells</td>
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<td>3:20 - 3:40</td>
<td>Faculty Meeting / Judging for Research Day Awards</td>
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Abbot F. Clark PHD

Keynote Speaker

Dr. Clark completed his Bachelor of Arts degree in biology at Thiel College and earned a doctorate in microbiology from Case Western Reserve University. He received post-doctoral training at the University of Texas Southwestern Medical Center in the departments of Microbiology (immunology) and Physiology (muscle metabolism) in Dallas.

Dr. Clark is a true leader in glaucoma research. He has served as vice president of Discovery Research and as head of Glaucoma Research at Alcon Laboratories. At these posts, Dr. Clark directed a broad range of high-impact glaucoma research that ranged from fundamental studies of trabecular meshwork and optic nerve biology to steroid-induced glaucoma.

Initially in parallel with his work at Alcon Laboratories, Dr. Clark has also had a highly productive academic career at the Health Science Center at the University of Northern Texas. More recently, after retiring from Alcon Laboratories, he has become the Director of the Visual Sciences Program at UNT and heads the North Texas Eye Research Institute. In this capacity, Dr. Clark has trained and mentored many leading researchers that have also gone on to make enormous contributions to ophthalmology.

Dr. Clark's research has provided major insights into the basic biochemical, cellular and molecular mechanisms involved in glaucoma pathophysiology. He continues to direct a highly innovative research program that includes molecular genetic and proteomic studies of glaucoma using cutting edge technologies including ocular cell culture, ex vivo organ culture, and rodent models of glaucoma. He has published more than 130 peer-reviewed manuscripts, 206 abstracts, authored 10 book chapters, given 68 invited seminars nationally and internationally, and he is an inventor of more than 60 patents.
Residents that have completed their Research Project

C. Blake Perry MD  
Supervisor: Richard C. Allen, MD, PHD  
Repair of 50-75% full-thickness lower eyelid defects: lateral stabilization as a guiding principle

Elizabeth Gauger, MD  
Supervisor: Vinit Mahajan, MD, PHD  
Management of Pediatric Aphakic Glaucoma with Vitrectomy and Tube Shunts

Pavlina Kemp, MD  
Supervisor: Thomas A. Oetting, MD  
Stability and Safety of MA50 Intraocular Lens Placed in the Sulcus

Angela R. McAllister, MD  
Supervisor: Michael D. Abramoff, MD, PHD  
Deviation from the optimal branching relationship of retinal vessels in diabetes mellitus

Justin M. Risma, MD  
Supervisor: Young H. Kwon, MD, PHD  
Diaton tonometry in patients with ocular hypertension, glaucoma, and glaucoma drainage devices—A preliminary study for its potential use in keratoprosthesis patients
Comparison of Early Changes in the Neuroretina to those in the Brain in Diabetes

P. Christi Carter, M.D.

Supervisors: James Folk, M.D.; Michael Abramoff, M.D., Ph.D.

Co-authors: Elliott Sohn, M.D.

Background/Purpose: Longstanding diabetes mellitus is associated with neurodegeneration in the retina (specifically in the ganglion cell layer and nerve fiber layer). Recent evidence indicates that longstanding diabetes mellitus is also associated with cognitive decline and cerebral atrophy. The exact cause of this cerebral atrophy is not yet known. This study seeks to determine if there is a correlation between neuronal degeneration in the brain to that in the retina. Given that the retina is an embryologic extension of the brain, it is biologically plausible that this may be the case. If a correlation is found, the retina would be an easily accessible structure to further study the cause and natural history of neuronal degeneration in the brain. Furthermore, optical coherence tomography (OCT) of the retina could potentially serve as a fast, cost-effective, and patient-friendly screening tool for brain damage in the future.

Methods: A cross-sectional pilot study will be performed in 100 patients with Type I diabetes mellitus of at least 15 years duration. OCT of the retina, fundus photography, magnetic resonance imaging (MRI) of the brain, and nerve conduction studies of the lower extremities will be obtained for each patient. Fully-automated segmentation algorithms (that have been previously validated) will be applied to the images obtained from OCT and MRI to quantify the thickness of specific layers in the retina and specific Brodmann areas in the brain, respectively. The brain and retinal measurements will be analyzed using a mixed model to determine if a correlation is present between neuronal degeneration in the brain and retina.

Results: Pending

Conclusion: Pending
Correlation of Structural Changes of Ganglion Cell Layer Thickness Analysis on Cirrus Optical Coherence Tomography and Functional Loss on Humphrey Visual Fields

Philip I. Niles, M.D., M.B.A.

Supervisor: Young Kwon, M.D., Ph.D.

Background/Purpose: Glaucoma is a progressive optic neuropathy in which there is a loss of retinal ganglion cells and their axons. Optical coherence tomography (OCT) is a high-resolution, micron-scale imaging modality that is capable of detecting progressive glaucomatous atrophy. The evolution from time domain OCT to spectral-domain OCT has allowed for higher resolution images and measurements of progressive glaucomatous changes in the ganglion cell layer. These quantitative measures provided by spectral domain OCT may serve as a useful adjunct to longitudinal assessment of visual function with standard automated perimetry (SAP) and optic nerve appearance using clinical examination and stereoscopic optic disc photography in detecting glaucoma progression.

Methods: Longitudinal, prospective data was collected on 98 glaucomatous and 30 glaucoma suspect eyes from the year 2008 to 2013. At each visit, patients underwent SAP and optical coherence tomography. SAP progression was monitored using mean deviation and pattern standard deviation parameters. The ganglion cell layer thickness was monitored using the Ganglion Cell Analysis (GCA) algorithm on the Cirrus OCT (Carl Zeiss Meditec Dublin, CA, USA). The change in the SAP will be compared to the change in the GCA. This will demonstrate

Results: Pending

Conclusion: Pending

Financial Disclosure: The authors have no financial interests to disclose.
Visual Noise in Glaucoma

Johanna Beebe, M.D.

Supervisor: Chris A. Johnson, M.Sc, Ph.D, D.Sc.

Co-authors: Elisabeth Aponte, M.D., A. Tim Johnson, M.D., Ph.D; Wallace L.M. Alward, M.D.; Young H. Kwon, M.D., Ph.D.

Background/Purpose: Glaucoma is known to not only affect cause damage to the optic nerve, but affects the macula as well. Given this it is possible that patients with glaucoma also experience decreased contrast sensitivity. The Pelli-Levi-Dual Acuity chart appears much like a traditional Snellen acuity chart, however it has six letters per row with three letter with no-noise and three letters with overlying visual noise. The purpose of this study is to determine effect of visual noise on visual acuity in patients with glaucoma.

Methods: The primary endpoint of the study will be the determination of visual acuity in glaucoma patient on visual acuity chart testing involving visual noise compared to visual acuity charts without visual noise. 40 patients will read a Pelli-Levi Dual-Acuity Chart and the results will be document. Tradition Snellen visual acuity, age, and type of glaucoma will also be recorded.

Results: Pending

Conclusion: Pending

Financial Disclosure: The authors have no financial interests to disclose.
Apraclonidine in the Diagnosis of Horner Syndrome: Development of Pupillary Adrenergic Supersensitivity after Pharmacologic Induction of Oculosympathetic Defect

Christopher A. Kirkpatrick, M.D.

Supervisor: Randy H. Kardon, M.D., Ph.D.

Background: The diagnosis of Horner Syndrome (HS) is based on miosis, ptosis and anhidrosis and can be equivocal, requiring confirmation with pharmacological eye drop testing. In recent years, apraclonidine, an alpha-2 agonist with weak alpha-1 properties, has gained acceptance over cocaine testing for the diagnosis of HS. This is due to its greater availability over schedule 2 drugs, and its ability to reverse anisocoria and ptosis as a result of its sympathomimetic alpha-1 receptor effect in the presence of adrenergic supersensitivity. However, criteria for a positive apraclonidine test for diagnosing HS have been lacking. A positive test is influenced by the development of alpha-1 adrenergic supersensitivity and its magnitude, which depends on the duration of the oculosympathetic deficit and the amount of deficit causing it.

Purpose: Criteria for a positive apraclonidine test for diagnosing HS were developed based on ocular responses to topical apraclonidine. In addition, the number of days required to develop adrenergic supersensitivity was determined using alpha-2 inhibition of norepinephrine release by topical brimonidine.

Methods: There were 3 methodological parts to this study.

Part I: Analysis of the ocular responses to apraclonidine in normal subjects.

Pupillary measurements in 100 normal healthy control subjects were obtained from digital infrared video frames before, 30 and 45 minutes after one drop of 0.5% apraclonidine OU in dim light. Pupillary responses were analyzed in millimeters and as a ratio of pupil/limbus (P/I ratio).

Part II: Determination of length of time needed for the development of adrenergic supersensitivity.

10 subjects from Part I were studied daily for 5 days. One drop of 0.2% brimonidine was given to the right eye (OD) twice daily to induce an oculosympathetic defect to study the development of adrenergic supersensitivity. The left eye (OS) was used as a control. The development of adrenergic supersensitivity was assessed by comparing the pupillary response of the right and left eye to one drop of 0.5% apraclonidine to both eyes (OU) as in Part I.
Adrenergic supersensitivity was considered present if a significant apraclonidine induced mydriasis occurred in the brimonidine-treated eye vs. the non-treated eye.

**Part III: Comparison of ocular responses to apraclonidine in a) patients with a clinical diagnosis of HS, b) patients with anisocoria but lacking a clinical diagnosis of HS and c) normal subjects.**

A retrospective chart review of patients seen at UIHC Department of Ophthalmology that have had apraclonidine testing – who may or may not carry the diagnosis of HS (based on cocaine testing, imaging or clinical objective criteria other than a positive apraclonidine test) – are being evaluated against the results in Part I to critically assess the sensitivity and specificity of the apraclonidine test and to propose objective criteria for its use to diagnose HS.

**Results:** Part I: The mean [± SD] change in pupil diameter (post -pre treatment pupil size) in dim light after administration of one drop 0.5% apraclonidine OU at 30 minutes was -0.410 ± 0.663 mm (range +2.6 - -1.93 mm) and was -0.538 ± 0.618 mm (range + 1.46 - -2.4 mm) at 45 minutes.

Part II: 4 of 10 subjects met criteria for the presence of adrenergic supersensitivity during the 5 day study period. The 4 subjects first demonstrated supersensitivity to apraclonidine in the brimonidine treated eye starting at 24, 48, 72, and 96 hours, respectively. The 6 subjects that did not reach criteria for supersensitivity during the 96 hour testing period all demonstrated a trend in that direction and may have eventually reached criteria for supersensitivity had the testing period been longer.

Part III: Pending

**Conclusions:** The results of this study suggest that detectable adrenergic supersensitivity of end-organs can develop as soon as 24 hours from the onset of a pharmacologically induced sympathetic blockade, but may take longer in some patients. Pupil responses to apraclonidine in normal subjects and in patients can be utilized to develop objective criteria for the diagnosis of HS.
Boston Type I Keratoprosthesis for Chemical and Thermal Injury

David L. Phillips, M.D.

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

Co-authors: Kenneth M. Goins, M.D.; Anna S. Kitzmann, M.D.; Mark A. Greiner, M.D.

Background/Purpose: To evaluate the outcome of the Boston keratoprosthesis type 1 (Kpro-1) in eyes with chemical and thermal injury.

Patients and Methods: A retrospective review was performed of every eye with a chemical or thermal injury that was treated with a Kpro-1 at a tertiary eye care center between January 1, 2008 and July 1, 2012. The main outcome measures were visual outcome, graft retention, and postoperative complications.

Results: Nine eyes met the inclusion criteria, including 7 eyes with alkali burns, 1 eye with an acid burn, and 1 eye with a thermal burn. After a mean follow-up of 40.7 months (range, 29-60 months), the median best corrected visual acuity was 20/60 (range, 20/15 to no light perception). One eye was ≥ 20/20, 3 eyes were ≥ 20/40, and 6 eyes were ≥ 20/70. The initial Kpro-1 graft was retained in 7 (77.7%) eyes, and successfully replaced in both cases. One or more serious complications occurred in 6 (66.7%) eyes. These included 2 cases of microbial keratitis (1 bacterial, 1 fungal), 2 cases of sterile corneal ulceration leading to graft extrusion, 2 cases of bacterial endophthalmitis, and 2 retinal detachments. These complications contributed to visual outcomes of hand motions in 2 eyes and no light perception in 1 eye.

Conclusions: The Boston Kpro-1 is associated with highly satisfactory visual improvement and graft retention in most cases of severe chemical or thermal injury. Serious complications are common and may threaten graft retention and/or compromise the visual outcome.

Financial Disclosure: The authors have no financial interests to disclose.
Boston Type I Keratoprosthesis for Failed Penetrating Keratoplasty

Jonathan Hager, M.D.

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

Co-authors: Kenneth M. Goins, M.D.; Anna S. Kitzmann, M.D.; Mark A. Greiner, M.D.

Background/Purpose: To evaluate and compare the outcomes of the Boston type 1 keratoprosthesis (Kpro-1) in eyes with one or more failed conventional keratoplasties.

Patients and Methods: A retrospective review was performed of the medical records of every patient treated with a Kpro-1 at University of Iowa Hospitals and Clinics between January 1, 2008 and July 1, 2012. Eyes with a failed keratoplasty that had originally been performed for corneal edema, trauma, or keratoconus were included in the statistical analysis. The main outcome measures were visual outcome, graft retention, and postoperative complications.

Results: Twenty four eyes met the inclusion criteria, including 13 eyes with corneal edema, 8 eyes with trauma, and 3 eyes with keratoconus. After a mean follow-up period of 28.9 months (range, 7 to 63 months), the median best corrected visual acuity (BCVA) was 20/125 (range, 20/30 to light perception). The BCVA was ≥ 20/40 in 4 (16.7%) eyes, ≥ 20/70 in 9 (37.5%) eyes, and ≥ 20/200 in 14 (58.3%) eyes. Overall, the postoperative BCVA improved in 17 (70.9%) eyes, was unchanged in 3 (12.5%) eyes, and was worse in 4 (16.7%) eyes. The initial Kpro-1 graft was retained in 22 (91.7%) eyes, and was successfully repeated in both cases. One or more serious graft- or sight-threatening complications occurred in 8 (33.3%) eyes. These included 1 case of wound dehiscence leading to graft extrusion, 1 case of fungal keratitis leading to graft extrusion, 4 cases of endophthalmitis, and 5 retinal detachments.

Conclusions: The Boston Kpro-1 is associated with an excellent prognosis for graft retention and satisfactory visual improvement in eyes with previous keratoplasty failure.

Financial Disclosure: The authors have no financial interests to disclose.
Treatment of Recalcitrant Acanthamoeba Keratitis with Intravenous Pentamidine Prior to Therapeutic Keratoplasty

Bradley A. Sacher, M.D.

Supervisor: Anna S. Kitzmann, M.D.

Co-authors: Michael D. Wagoner, M.D. Ph.D.; Kenneth M. Goins, M.D.; John E. Sutphin, M.D.; Mark A. Greiner, M.D.

Background/Purpose: Acanthamoeba keratitis is a serious sight threatening condition that often fails to respond to topical and systemic anti-amoebic medications. An attempted cure with a therapeutic keratoplasty (TKP) is often associated with recurrent infection and/or graft failure. The purpose of this study is to evaluate the outcome of pre-treatment of eyes with medically or surgically-recalcitrant Acanthamoeba keratitis with intravenous (IV) pentamidine prior to TKP.

Methods: A retrospective chart review was performed of the medical records of every patient treated with Acanthamoeba keratitis at University of Iowa Hospitals and Clinics between January 1, 2002 and December 31, 2012. Eyes that were treated with intravenous pentamidine prior to TKP were included in the statistical analysis.

Outcome Measures: The main outcome measures were microbiological cure, therapeutic graft survival, and visual outcome.

Results: Eight eyes of 7 patients met the inclusion criteria. Preoperatively, all 8 eyes had failed traditional anti-amoebic therapy, including 4 with recurrent infection after a previous TKP. Prior to initiation of pentamidine therapy and performance of a TKP, 6 (75.0%) eyes had best corrected visual acuity (BCVA) that was ≤ 20/200, including 3 eyes that were hand motions (HM) or worse. The median interval between presentation and initiation of pentamidine therapy was 5.3 months (range, 2.1 to 12.8 months). Patients were treated with IV pentamidine (190 to 400 mg/day) for 7 to 26 days. After 8 TKP, a microbiological cure was achieved in 7 (87.5%) eyes. Six (75.0%) grafts remained clear at the most recent follow-up examination. The final BCVA was ≥ 20/40 in 4 (50.0%) eyes and ≥ 20/70 in 5 (62.5%) eyes. Three (37.5%) eyes were ≤ 20/200, including one eye that was HM (failed graft) and one that was no light perception (recurrent infection and enucleation).
Conclusions: The adjunctive use of preoperative IV pentamidine may be effective in reducing the incidence of recurrent infection and graft failure after TKP in eyes with recalcitrant Acanthamoeba keratitis.

Financial Disclosure: The authors have no financial interests to disclose.
Reversibility of Glaucomatous Visual Field Defects

Jesse M. Vislisel, M.D.

Supervisors: Michael Wall, M.D.; Wallace L.M. Alward, M.D.

Background/Purpose: It is a widely-held belief that glaucomatous visual field loss is irreversible and that the goal of management is to stabilize or slow further loss as much as possible. This study seeks to determine whether the visual field in glaucoma patients can improve beyond what is expected with the perimetric learning effect, and if so, what factors of the disease and treatment regimens may correlate with this improvement.

Methods: 60 normal and 120 glaucoma patients were tested with three separate visual field procedures including SITA size III automated perimetry, full threshold size V automated perimetry, and Humphrey Matrix perimetry. Measurements were taken twice at baseline and then every 6 months for 4 years. Mean defects from each test were plotted over time and a slope between the points was determined for each visual field test for each subject. The normal subjects were used to calculate 95% confidence intervals (CI) for the mean defect slope. These normal confidence intervals were then used to divide the glaucoma patients into 3 groups, those with at least 1 mean defect slope above the upper 95% confidence limit, those with at least 1 below the lower 95% confidence limit, and those with all results lying within the 95% confidence interval. A retrospective analysis was then conducted to make comparisons between the features of these groups.

Results: Pending.

Conclusion: Pending.
Prophylactic Povidone-Iodine Rinses and Topical Amphotericin-B Significantly Reduce Postoperative Infections after Boston Type I Keratoprosthesis

Jeffrey D. Welder, M.D.

Supervisor: Mark A. Greiner, M.D.

Co-authors: Michael D. Wagoner, M.D., PhD; Kenneth M. Goins, M.D.; Anna S. Kitzmann, M.D.

Background/Purpose: The incidence of graft- and sight-threatening microbial keratitis and endophthalmitis after Boston type 1 keratoprosthesis (Kpro-1) was reduced with the introduction of chronic daily anti-bacterial prophylaxis. However, infections with resistant bacteria and fungi remained a relatively common threat to graft retention and visual rehabilitation, thereby necessitating the institution of more aggressive prophylactic polymicrobial regimens. The purpose of this study is to compare the incidence of postoperative infections between eyes treated with vancomycin and fluoroquinolone prophylaxis alone versus those treated with additional polymicrobial prophylaxis using povidone-iodine rinses and topical amphotericin-B.

Methods: A retrospective review was performed of the medical records of every patient treated with a Boston Kpro-1 at UIHC between December 2008 and January 2014. For statistical analysis, eyes were divided into three groups according to the prophylactic antimicrobial regimen: treatment with daily vancomycin and a fluoroquinolone antibiotic alone (group 1); treatment with additional quarterly povidone-iodine 5% fornix rinses (group 2); and treatment with additional quarterly povidone-iodine 5% fornix rinses and a 1-week course of topical amphotericin B 0.15% (group 3).

Outcome Measures: The main outcome measure was the incidence of postoperative infections, as defined by the number of cases of microbial keratitis and/or endophthalmitis per year. Secondary outcome measures were Kpro-1 retention and visual outcome in eyes with and without postoperative infections.

Results: Seventy-nine eyes of 78 patients met the inclusion criteria. There were 33,532 postoperative operative follow-up days in group 1, 16,185 follow-up days in group 2, and 28,317 follow-up days in group 3. The incidence of postoperative infections was 0.13/year in group 1, 0.09/year in group 2, and 0.01/year in group 3 ($P < 0.05$). In group 1, there were 12 postoperative infections, including 4 cases of microbial keratitis (2 bacterial, 2 fungal) and 8 cases of endophthalmitis (6 bacterial, 1 fungal, 1 culture-negative). In group 2, there were 4 postoperative infections, including 3 cases of microbial keratitis (1 bacterial, 2 fungal) and 1 case of bacterial endophthalmitis. In group 3, there was 1 case of culture-negative keratitis. Kpro-1 extrusion occurred in 6
(35.3%) of 17 eyes with postoperative infections, but not in any of the 62 non-infected eyes \((P = 0.0002)\). At the most recent examination, the median best corrected visual acuity was counting fingers among eyes with postoperative infections, compared to 20/125 in those without infections \((P = 0.13)\).

**Conclusions:** Quarterly polymicrobial povidone-iodine rinses and topical amphotericin-B, in combination with daily antibacterial prophylaxis, significantly reduces postoperative infections after KPro-1, thereby improving the prognosis for graft retention and visual outcome.

**Financial Disclosure:** The authors have no financial interests to disclose.
Brown Syndrome Outcomes at the University of Iowa Hospitals & Clinics: A Forty-Year Retrospective Analysis

Matthew C. Weed, M.D.

Supervisor: Scott A. Larson, M.D.

Co-authors: Susannah Q. Longmuir, M.D.

Background/Purpose: To evaluate the results of surgical and non-surgical treatment of Brown syndrome at the University of Iowa Hospitals & Clinics

Methods: A retrospective chart review was performed on 305 patient charts with a clinical diagnosis of Brown syndrome, hypotropia, or hypertropia that presented to the Pediatric Ophthalmology and Strabismus service between 1 January 1973 and 31 December 2012. The inclusion criterion was a documented clinical diagnosis of Brown syndrome. Iatrogenic cases (i.e. those that developed Brown-like syndrome after strabismus surgery for a different indication) were excluded. Other causes of hypotropia or hypertropia (e.g. superior oblique palsy, monocular elevation deficiency, thyroid eye disease) were also excluded. The main outcome measures were change in supraduction limitation in the affected eye, change in vertical strabismus in primary gaze, and preferred head position.

Results: 75 patients met inclusion criteria. The mean age at presentation was 11.4 years, with a range of 3 months to 77 years. The mean follow-up was 3.62 years, with a range of 0 to 20.8 years. 27 patients (36%) were male and 48 (64%) were female. 37 patients (49%) were affected in the right eye; 30 patients (40%) were affected in the left eye; eight patients (11%) were affected in both eyes. 53 cases (71%) were congenital onset; 16 cases (21%) were acquired; disease onset could not be determined in 6 cases (8%). 15 patients (20%) were treated for amblyopia. Of the 53 congenital cases, 11 (21%) were treated surgically whereas 42 (79%) were treated non-surgically.

Among the congenital Brown patients treated surgically, the mean preoperative supraduction deficit in the affected eye was -4.1 (SD 1.04), and the mean postoperative deficit was -1.4 (SD 1.63), a statistically significant difference (p=0.0051). Among these same patients, the mean preoperative hypotropia in the affected eye in primary gaze was 13.7 prism diopters (SD 7.25), and the mean postoperative vertical tropia was 0.1 prism diopters of hypertropia (SD 2.39), a statistically significant difference (p=0.0034).

Among congenital patients treated non-surgically, the mean supraduction deficit in the affected eye on presentation was -3.0 (SD 1.04), and the mean final deficit was -3.4 (SD 1.28), a non-statistically significant difference (p=0.60). In this group, supraduction improved in 13%, worsened in 3% and remained unchanged in 83%.
Among the 53 patients with congenital Brown syndrome, 34 (64%) presented with an abnormal head position (AHP), most commonly a head turn (25 patients) or a chin-up (17 patients). Of the 34 patients presenting with an AHP, 25 (74%) were observed. Among this group, the AHP resolved in 4 patients (16%), and persisted in the other 21 (84%) at time of last follow-up. Of the 9 patients presenting with an AHP who were treated surgically, the AHP resolved in 6 (67%) and persisted in 3 (33%). The difference in rate of resolution of AHP among the patients with congenital Brown syndrome treated surgically versus those treated non-surgically was statistically significant (p=0.0088).

There were 13 acquired Brown syndrome patients treated non-surgically. In this group 4 (31%) improved, 1 (8%) worsened and 8 (62%) remained unchanged. 3 of the 4 that improved had inflammatory conditions that caused the Brown syndrome.

A multivariate analysis was performed to identify factors that correlated with change in supraduction deficit over time. Superior oblique surgery was found to have a significant correlation with improved supraduction deficit. Gender, amblyopia treatment, use of glasses, the presence of horizontal strabismus, and time of follow-up all demonstrated no correlation with improvement or worsening.

**Conclusions:**
1. Recent reports on Brown syndrome suggest that most patients improve spontaneously. Our data suggest that although some do improve, the vast majority remain stable.
2. The most important factor predicting improvement in supraduction was surgery of the superior oblique tendon.
3. Patients with abnormal head positions in Brown syndrome were more likely to adopt a head turn than a chin up position.
4. In congenital cases, gender, amblyopia treatment, the use of glasses, and the presence of horizontal strabismus were not helpful in predicting spontaneous improvement or worsening.

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Factors Associated with Spontaneous Release of Vitreomacular Traction

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Background: Vitreomacular traction (VMT) has been increasingly recognized as a cause of central vision loss and has attracted increased attention as a target for both surgical and pharmacologic treatments. Serial observations have confirmed that the attachment of the vitreous to the macula will separate spontaneously in some cases. It is not known however, what factors, if any, might predict or be associated with this spontaneous separation and resolution of the traction.

Purpose: To analyze the factors that may predict the release of VMT and vitreomacular adhesion (VMA).

Methods: Retrospective case-control study involving 61 patients with VMT imaged by optical coherence tomography (OCT) over at least three months. Records from all patients seen at the University of Iowa from January 2012 to September 2013 were screened for the ICD9 code for VMT, VMA and epiretinal membrane (379.27 and 362.56). These medical records were reviewed to confirm inclusion criteria of the diagnosis of VMT or VMA by OCT and three months of imaging follow-up. OCT of subjects with VMA or VMT were characterized as broad (>400 microns) or focal (<400 microns) adhesions and as isolated inner retinal or inner/outer retinal distortion. Subjects were also characterized as receiving contemporaneous vitreous injections or not. Release of VMT (R-VMT) was defined by resolution of patients’ symptoms or traction by OCT without surgical intervention or ocriplasmin injection. Individual factors or characteristics were evaluated by chi-square test. Using a binary logistic regression model, the potentially prognostic factors were evaluated for contribution to R-VMT.

Results: Of the 61 patients that met entry criteria, 21 (35%) developed R-VMT during OCT follow-up and 40 (65%) did not. Isolated inner retinal distortion without outer retinal involvement was significantly associated with R-VMR (p=0.01). Vitreous injections were also associated with R-VMR (p=0.02).

Conclusion: Eyes with VMT and isolated inner retinal distortion and those receiving vitreous injections are more likely to develop VMT release without the need for surgical intervention or ocriplasmin treatment.

Disclosure Almeida: Allergan (H), Alcon (H), Genentech (H), Novartis (H). Other authors: None
Correlation of decreased contrast sensitivity in glaucoma patients and glaucoma suspects to ganglion cell layer analysis on Cirrus OCT

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Background/Purpose: Glaucoma has been classically described as an optic neuropathy with characteristic changes in cupping and perimetry. However, more recently, the macula has also been found to be involved in the pathophysiology of glaucoma, with many publications reporting thinning of the macular ganglion cell complex in glaucoma patients. There has been limited progress in developing tests of functional deficits (visual performance) evaluating the macula of glaucoma patients. The visual acuity in noise eye chart has demonstrated an ability to identify functional visual loss that has not been detected by conventional visual acuity tests, but its role in glaucoma has not yet been assessed. The purpose of this study is to determine the effect of the visual noise in acuity testing in patients with glaucoma and to correlate these findings to Cirrus macula optical coherence tomography. We hypothesize that this procedure will be effective in identifying heterogeneous ("patchy") loss in the macula of glaucoma patients.

Methods: Forty patients with glaucoma or suspicion for glaucoma will have their visual acuity determined with and without noise using the Dual-Acuity Pelli-Levi chart. The visual noise data will then be correlated to Cirrus macula optical coherence using the retinal ganglion cell complex measurements.

Results: This is a pilot study and we estimate that 40 patients will be sufficient to give us preliminary data on visual acuity noise for glaucoma patients.

Conclusion: The clinical advantages and disadvantages of this procedure will be determined by this research, as well as the importance of structure-function relationships in the macula of glaucoma patients and the significance of asymmetries between two eyes of any particular patient.

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Etiology and Prognosis of Central Vision Loss at Presentation in Idiopathic Intracranial Hypertension

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Background/Purpose: Early central vision loss in idiopathic intracranial hypertension (IIH), while not common, can result from different mechanisms, including subretinal fluid, papilledema/optic neuropathy, choroidal folds, hyperopic shift, macular hemorrhages macular edema, or rarely subretinal neovascularization. The mechanism of the visual loss is important to determine to help guide management decisions, such as the need for early surgical intervention. This study examines the etiology and prognosis of central vision loss in IIH at presentation, and provides objective measures to predict visual outcomes.

Methods: A retrospective review of 660 patients with IIH (2009 - 2013) identified 33 patients (5%) with best-corrected visual acuity of 20/25 or worse on presentation. Fundus photography, spectral-domain optical coherence tomography (OCT) of the disc and macula, and perimetry were used to determine the causes of central vision loss and evaluate visual prognosis. Segmentation of the macula OCT was performed with the Iowa Reference Algorithm to determine the retinal ganglion cell-inner plexiform layer complex (GCL-IPL) thickness and subretinal fluid volume. The correlation between the subretinal fluid volume and visual acuity was examined. GCL-IPL thinning on OCT was considered indicative of optic neuropathy as a contributor to central vision loss.

Results: Outer retinal changes alone caused decreased central vision in 13 patients: subretinal fluid in 9, chorioretinal folds in 3, and peripapillary choroidal neovascularization in 1. The vision loss was reversible except in the patients with chorioretinal folds. Papilledema/optic neuropathy alone caused decreased central vision in 9 patients. Co-existing outer retinal changes and optic neuropathy caused central vision loss in 11 patients, whose outcome was largely dependent on the degree of optic neuropathy. A GCL-IPL thickness of less than 70 µm or early progressive thinning of more than 10-15 µm compared to baseline were suggestive of poor visual outcome.

Conclusion: Central vision loss in IIH can be caused by both outer retinal changes and optic neuropathy. Vision loss from outer retinal changes is mostly reversible. The outcome of patients with co-existing outer retinal changes and optic neuropathy or optic neuropathy alone is dependent on the degree of optic neuropathy, which can be predicted by the GCL-IPL thickness.
References:


Oral Mineralocorticoid Antagonists for the Treatment of Central Serous Chorioretinopathy

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Supervisor: James C. Folk, M.D.


Background/Purpose: To evaluate the effect and tolerance of oral mineralocorticoid antagonists, eplerenone and/or spironolactone, in central serous chorioretinopathy (CSCR).

Design: Retrospective, observational case series.

Methods: The medical records of 120 patients with CSCR were reviewed. Twenty-nine patients who were treated with one or more mineralocorticoid antagonists were observed. Primary outcome measures included changes in central macular thickness (CMT, µm), macular volume (MV, mm$^3$), and Snellen visual acuity. Secondary outcomes included duration of treatment, treatment dosage, systemic side effects, and prior treatment failures.

Results: The average age was 58.4 years old and fifteen (65.2%) were male. Nine patients (39.1%) had prior exogenous steroid use. Sixteen patients (69.6%) were previously treated with other interventions before oral mineralocorticoid antagonists. The average duration of treatment was 3.9 ± 2.3 months. Twelve patients (52.2%) showed decreased CMT and MV, six patients (26.1%) had increased in both, and five patients (21.7%) had negligible changes. The mean decrease in CMT was 42.4 µm (range, -136 to 255 µm), and the mean decrease in MV was 0.20 mm$^3$ (range -2.33 to 2.90 mm$^3$). Median visual acuity at the start of therapy was 20/30 (range, 20/20 – 20/250), and at final follow-up 20/40 (range, 20/20 – 20/125). Nine patients (39.1%) experienced systemic side effects, of which three patients (13.0%) were unable to continue therapy.

Conclusion: Mineralocorticoid antagonist treatment had a positive treatment effect in half of our patients who did not respond to other therapies. Systemic side effects, even at low doses, may limit its usage in some patients.

Financial Disclosure: Unrestricted grant from the VitreoRetinal Surgery Foundation (VRSF).
**PAX6-associated Congenital Cataracts without Aniridia**

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**Background/Purpose:** Deletions of *PAX6* are known to cause aniridia syndrome, which may include congenital cataracts. Point mutations may result in milder phenotypes. We investigated the incidence of *PAX6* point mutations in congenital cataract patients without obvious aniridia.

**Methods:** From 2008-2013 congenital cataract patients at the University of Iowa Pediatric Ophthalmology service were offered screening of potential cataract genes. DNA was extracted from peripheral blood and *PAX6* exons 3-14 were sequenced. Variants were searched in the Exome Variant Server (EVS). Retrospective chart review was performed for genotype-phenotype correlation.

**Results:** 23 patients were enrolled. 19 had *PAX6* sequencing. 11 had autosomal dominant (AD) family history. Disease-causing mutations were found in 3/11 AD patients and none of the others. *PAX6* mutations segregated with cataract in the families. 2 probands had iris transillumination defects, 1correctopia, 2/3 foveal hypoplasia. All three had nystagmus. None of the patients found to have *PAX6* mutations were found to have glaucoma.

**Discussion:** Because of grossly normal iris appearance, our patients were not suspected to have aniridia before genetic testing. Visual prognosis of children with congenital cataracts varies. Identifying patients with *PAX6*-associated cataracts alerts clinicians to other ocular anomalies, improves prognostic accuracy and guides management and genetic counseling. No statistically significant physical exam findings distinguished these patients from patients without *PAX6* mutations. However all *PAX6* patients had AD inheritance and nystagmus, and none had glaucoma. Several non-disease-causing polymorphisms for the *PAX6* gene exist.

**Conclusion:** Although our sample is small, the presence of 3 AD families with *PAX6* mutations among the first 19 families tested suggests this may be a more common cause of apparently isolated congenital cataracts than previously believed. Congenital cataract patients who develop nystagmus despite timely surgery may have *PAX6* mutations. We recommend *PAX6* analysis in autosomal dominant congenital cataract, especially if accompanied by other findings such as nystagmus or foveal hypoplasia.
References:
Cystoid macular edema and glaucoma filtration surgery

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Background/Purpose: To evaluate the effect of glaucoma filtration surgery (GFS) on cystoid macular edema (CME).

Methods: A retrospective case series was assembled from patients who had both CME and a history of GFS. Past ocular and medical history were reviewed for each patient. Visual acuity, intraocular pressure, presence or absence of anterior chamber cell and flare and vitreous cells, macular thickening on slit lamp exam or central macular thickness on optical coherence tomography, and treatment plan were reviewed for the preoperative visit and each postoperative visit. The administration schedule of intraocular and periocular steroids and intraocular anti-vascular endothelial growth factor were also reviewed.

Results: Nineteen glaucoma filtration surgeries performed on 16 eyes from 16 patients were reviewed. One was a trabeculectomy and the others were either Ahmed (12) or Baerveldt (6) seton devices. Follow-up ranged 5 months to 4 years. In 16/19 of the cases, the patients had a history of CME prior to GFS. Two of these patients had preexisting diabetic macular edema and the others had posterior uveitis of various etiologies. Of the cases with a history of CME, it worsened or recurred postoperatively in 6/16 cases. Seven out of 9 of the cases with no worsening and a history of CME received intraocular or periocular anti-inflammatory medication prior to or during surgery. All, but one of these were a fluocinolone acetonide implant. Only one of the 7 cases with worsening was treated with a fluocinolone acetonide implant perioperatively. Six out of 7 cases with worsening had CME at the time of surgery and only 3 cases with no CME postoperatively had CME at their preoperative visit. Three patients developed CME for the first time after GFS and had no known risk factors for CME.

Conclusions: Glaucoma filtration surgery may be associated with worsening of preexisting CME and induce the onset of CME in patients with no known history. The presence of CME at the time of surgery seemed to be a risk factor for worsening after GFS. Our review also suggested that patients treated with an intraocular implant of high dose steroid, such as fluocinolone acetonide may be less likely to develop CME following GFS.

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One Year Clinical Outcomes Of A Randomized Clinical Trial Investigating Pre-operative Adjunctive Bevacizumab For Tractional Retinal Detachment (TRD) Due To Proliferative Diabetic Retinopathy (PDR)

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Background/Purpose: The utility of pre-operative bevacizumab for traction retinal detachment (TRD) due to proliferative diabetic retinopathy (PDR) remains contested due to the risk of TRD progression versus the benefit of attenuation of neovascularization. We sought to determine whether intra- and post-operative complications are decreased in eyes given pre-operative bevacizumab in eyes undergoing TRD surgery and if this corresponds to improved visual results. Preliminary three month post-operative data of this study has been published. In this study, we detail one-year clinical follow-up of this now completed study.

Methods: 20 eyes of 19 patients were randomized to receive intravitreal bevacizumab injection or sham injection 3-7 days prior to vitrectomy for TRD repair and definitive PDR treatment in a large urban, public hospital. Best-corrected visual acuity (BCVA), need for additional procedures, and postoperative complications were compared in the two groups at 6 and 12 month post-operative follow-up.

Results: Median BCVA in the control group was 20/400 at baseline, 20/633 at post-op month 3 (POM3), 20/168 at POM6, and 20/237 at POM12. The median BCVA in the treated group was 20/499 at baseline, 20/100 at POM3, 20/400 at POM6, and 20/150 at POM12. Three of seven eyes (43%) randomized to bevacizumab had the same or improved VA at POM12 compared to five of eight eyes (38%) in the control group.

All retinas were attached at POM12, but 6 eyes (3 in each group) had decreased VA compared to baseline. In the treatment arm, 1 patient had persistent cystoid macular edema (despite postoperative bevacizumab), 1 had ischemic changes postoperatively, and 1 had a visually significant cataract awaiting surgery. In the control arm, 1 patient had recurrent epiretinal membrane and 2 developed NLP vision despite retinal attachment: one from glaucoma and another from severe ischemia. During 12 month follow-up, 1 eye in each group needed repeat surgery for recurrent retinal detachment. No eye required enucleation.

Conclusions: Most eyes in this study experienced at least stable VA at one year follow-up. Need for additional surgical procedures for recurrent detachment is uncommon. The poorest visual outcomes were observed in the control group, but a series with a larger number of patients is required to confirm this finding.
References:


Conjunctival biopsy for lichen planus in lacrimal drainage obstruction

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Background/Purpose: Lichen planus is an autoimmune disease typically involving the skin and orogenital mucosa. Cicatrizng conjunctivitis and lacrimal drainage obstruction have been reported in patients with systemic lichen planus\textsuperscript{1,2}. Isolated conjunctival lichen planus is rare. The utility of conjunctival biopsy to diagnose isolated lichen planus of the lacrimal drainage system is unknown.

Methods: Patients who underwent conjunctival biopsy for an indication of lacrimal drainage obstruction were identified via retrospective review of cases submitted to our ocular pathology laboratory between December 2012 and July 2013. Patients that did not have tissue sent for direct immunofluorescence were excluded.

Results: Of 15 patients, 14 had a stromal lymphocytic infiltrate on histologic examination. Ten had basement membrane fibrinogen present on direct immunofluorescence testing. Five of these demonstrated shaggy fibrinogen morphology. IgG, IgA, IgM, and C3 were negative in all cases. None had systemic lesions or cicatrizng conjunctivitis.

Discussion: The detection of fibrinogen in the basement membrane of skin and orogenital mucosa is diagnostic for lichen planus. In contrast, linear fibrinogen is a normal finding of conjunctival epithelium. Abnormal morphology including shaggy, fragmented, or reduplicated basement membrane fibrinogen has been described in conjunctival lichen planus\textsuperscript{3}. Five of our cases demonstrated shaggy fibrinogen morphology which may indicate lichen planus underlying lacrimal drainage obstruction.

Conclusion: Only small studies have evaluated basement membrane fibrinogen in normal and inflamed conjunctiva\textsuperscript{9}. Further investigation is needed to determine if shaggy fibrinogen morphology is specific for lichen planus or if it may be seen in other etiologies of conjunctival inflammation.
References:


Limbal-Trocar Cannulas for Complex Vitrectomy Surgery

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Supervisor: Vinit B. Mahajan, M.D., Ph.D.

Background/Purpose: To review vitrectomy cases using limbus-based 25 and 23-gauge trocar-cannulas.

Design: Retrospective, interventional case series

Methods: Twenty-nine consecutive patients undergoing small-gauge vitrectomy trocar-cannulas at the limbus were examined. Operative techniques, surgical indications, and postoperative course were examined.

Results: Limbus-based trocars/cannulas were inserted into the anterior chamber during vitrectomy in 29 eyes with various and anterior segment pathology and posterior segment indications. These included: vitreous hemorrhage (3/29), retinal detachment (1/29), retained lens material (3/29), endophthalmitis (11/29), cataract extraction (6/29), pupillary membrane (1/29), epiretinal membrane (2/29), choroidal hemorrhage (3/29), pars plana tube insertion (1/29), nonclearing vitreous hemorrhage or media opacity (2/29). There were 29 adult eyes. Prior to surgery, 6 of the eyes were aphakic, 13 phakic, and 10 pseudophakic. 23-gauge instruments were used in 18 eyes and 25-gauge instruments in 11 eyes. Mean postoperative follow-up duration was at least three months. Anterior segment complications were not observed during surgery, or at any of the follow-up examinations.

Conclusion: Small-gauge vitrectomy trocar cannulas may be safely used through the anterior chamber during vitrectomy. The limbal approach for vitrectomy may be advantageous in complex cases where surgeons must avoid potential complications associated with pars-plana incisions or preserve scleral and conjunctival integrity.
Diabetes Mellitus Increases Risk of Unsuccessful Graft Preparation in Descemet’s Membrane Endothelial Keratoplasty

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Supervisor: Mark A. Greiner, M.D.


Background/Purpose: Descemet’s membrane endothelial keratoplasty (DMEK) is an increasingly popular transplant technique that achieves superior visual results and maximizes the speed of visual recovery in the treatment of corneal endothelial dysfunction. Graft preparation has been a barrier to widespread adoption of DMEK surgery, due to the delicate nature of the tissue and the risks of tissue destruction during the process. Experienced eye bank technicians at Iowa Lions Eye Bank observed anecdotally that DMEK tissue preparation resulted in tears and was more difficult to perform in donors with a history of diabetes mellitus. The purpose of this study was to evaluate preparation outcomes of tissue prepared for Descemet’s membrane endothelial keratoplasty (DMEK) from diabetic and non-diabetic donors.

Methods: We performed a multicenter, retrospective analysis of DMEK grafts prepared from diabetic and non-diabetic donors. Preparations were performed by experienced technicians at two Eye Bank Association of America accredited facilities using a modified submerged manual preparation technique to achieve “pre-stripped” graft tissue.

Outcome Measures: The main outcome measure was unsuccessful (failed) DMEK graft preparation, defined as tears through the graft area preventing tissue use. The secondary outcome measure was the difficulty of DMEK graft preparation, defined as time out of storage media for successful preparations.

Results: A total of 359 corneas prepared from 290 donors (114 diabetic, 245 non-diabetic) were included in the statistical analysis of graft preparation failure. There were no significant differences between diabetic and non-diabetic donor tissue characteristics with respect to donor age, death-to-preservation time, death-to-preparation time, endothelial cell density, percent hexagonality or coefficient of variation. DMEK tissue preparation was unsuccessful in 19 (5.3%) cases. There was a statistically significant difference in the site-adjusted rate of DMEK preparation failure between diabetic donors (15.3%; 95% CI 9.0, 25.0) and non-diabetic donors (1.9%; 95% CI 0.8, 4.8) (P = 0.001). The site-adjusted odds ratio of DMEK graft preparation failure in diabetic versus non-diabetic donor tissue was 9.20 (95% CI 2.89, 29.32). There was a statistically significant difference in the site-adjusted processing time for successful DMEK tissue preparation between diabetic donors (25:36 ±0:48) and non-diabetic donors (22:42 ±0:36) (P = 0.009).
Conclusion: Diabetes is a significant risk factor for unsuccessful preparation of donor tissue for DMEK. In addition, successful preparation from diabetic donors may be technically more difficult. We recommend caution in the use of diabetic tissue for DMEK graft preparation. Further study is needed to identify whether subsets of diabetic donors, such as those with higher HbA1C or longstanding disease, may be at more risk for unsuccessful preparation compared to diabetics in general.

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The Quantitated Internal Suture Browpexy or “chicken” Brassiere Suture

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Supervisor: Richard C. Allen, M.D., Ph.D.

Background/Purpose: Blepharoplasty in the setting of mild brow ptosis has been shown to result in brow depression (2,3). Numerous procedures are available to the surgeon to prevent brow depression, and an internal browpexy is attractive due to the lack of an additional external incision and relative technical ease. However, the effectiveness of a browpexy is questionable. Recently, a brassiere suture to enhance brow contour has been proposed (4), but lagophthalmos precludes some from adapting this technique. The purpose of this study is to evaluate the results of an internal suture browpexy, which quantitates the placement of the suture in relation to the superior orbital rim and upper blepharoplasty incision, thus combining the advantages of a browpexy and brassiere suture.

Methods: This study is a retrospective case review of all patients who underwent upper eyelid blepharoplasty and internal suture browpexy at the University of Iowa Hospitals and Clinics from 2009 to 2014.

Results: Thirty-nine patients were identified who underwent the above procedure. Effectiveness of the procedure was determined by the lack of post-operative brow descent. Twenty-two of 39 patients were female. The average age was 67.2 years. Pre-and post-operative photos at a mean of 4.0 months follow-up using the ImageJ 1.47v software (Wayne Rasband, National Institutes of Health, Bethesda, MD) were analyzed (final results pending).

Conclusions: Although a browpexy is a weak brow elevation procedure, it is useful in mild degrees of brow ptosis in patients who undergo upper blepharoplasty to prevent brow descent and to maintain adequate eyelid position for preventing exposure keratopathy. Quantitation of suture placement enables the establishment of a conservative, or “chicken” brassiere.

References:


Neuro-ophthalmology Does Windows! Evaluation of Confocal Corneal Microscopy in Normal Subjects, Diabetics and Patients with Neurotrophic Cornea

John Brinkley M.D.

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Co-authors: Brice Critser B.S., Jan Full R.N., Michael Wagoner M.D., Ph.D.

Background/Purpose: Patients with peripheral neuropathy or trigeminal nerve injury are at risk for developing neurotrophic cornea, which may lead to corneal epithelial erosions, corneal ulcers and permanent visual loss. New methods of quantifying corneal innervation in vivo using confocal microscopy may aid in the diagnosis and evaluation of new treatments for peripheral neuropathy.

Methods: Corneal confocal microscopy (Heidelberg HRT, Heidelberg, GE) was used to collect a stack 40 images every 2 microns (400x400x 80 micron volume) from the central cornea of each eye of 10 normal subjects, 9 subjects with diabetes, and 2 subjects with unilateral trigeminal damage seen in our neuro-ophthalmology clinic. Corneal confocal microscopy was repeated 5 times in each eye on 5 different days in the normal and diabetic subjects to determine measurement variability of the summed nerve branches using an automated 3D software analysis.

Results: The total micron nerve length in the central corneal including all branches (mean±SD) for normal subjects was 2064±489 (OD), 2019±477 (OS), and 66±727 (OD-OS). For diabetic subjects, 1993±533 (OD), 2038±481 (OS) and 44±733 (OD-OS), not significantly different from normal. Patient 1 with a neurotrophic cornea after optic nerve sheath fenestration had no nerves that could be visualized in that eye. Patient 2 with a prior Wallenberg syndrome showed significantly reduced ipsilateral nerve length. Anterior segment SD-OCT of the corneas in these two patients revealed no significant inter-ocular asymmetry in the measured epithelial or stromal thickness compared to the normal subjects.

Conclusions: Neurotrophic cornea from damage to the proximal or distal trigeminal nerve results in a dramatic loss of corneal nerves in the sub-epithelial basal plexus. Confocal microscopy can easily identify such differences, but subtle changes over time in progressive peripheral neuropathy (i.e. diabetic neuropathy) would not be detectable until at least half of the total nerve length is lost, as visualized by confocal microscopy.
Investigating the Influence of Blast on Cellularity in the Retinal Ganglion Cell Layer in a Mouse Model of Blast-induced Traumatic Brain Injury Using a Semi-automated Technique

Adam Hedberg-Buenz

Supervisor: Michael G. Anderson, Ph.D.

Co-authors: Mark Christopher, Laura Dutca, Todd Scheetz, Randy Kardon, M.D., Matt Harper, Ph.D.

Background/Purpose: Blast-mediated injuries are the leading cause of combat-related injury in modern warfare. Visual dysfunction has been reported in Veterans with blast-mediated traumatic brain injury (TBI). We have previously shown retinal ganglion cells (RGC) are susceptible to blast. However, the timeframe and magnitude of RGC loss after TBI is not yet understood. The axons and dendrites of RGC extend outside the ganglion cell layer (GCL), therefore we focused our analyses on the ganglion cell complex (GCC). The purpose of these experiments is to develop a robust method to quantify cellularity and investigate the influence of blast on the GCC after blast-induced TBI.

Methods: Two cohorts of age- and gender-matched C57BL/6J mice (n=12 each) were exposed to an overpressure wave (20 PSI) directed to the head using a custom-built blast chamber (blast-injured). Mice placed in the chamber without blast were used as sham controls. Spectral domain optical coherence tomography (SD-OCT) was used to measure thickness of the GCC in retinas of blast-injured and control mice both before and after exposure to blast. At 4 months post-blast, retinas from both blast-injured and control eyes were mounted whole, stained, and imaged by light microscopy. Images were uniformly collected across the entire retinal area with equal sampling from both the central and peripheral retina. Images were analyzed using custom-written macros in Image J for quantitative assessment of cellularity in the GCL.

Results: Retinas from blast-injured mice exhibit a significant decrease in GCC-thickness compared to pre-blast thickness (p<0.05, ANOVA), and sham controls at 4 months post-blast (p=0.003). A semi-automated technique using ImageJ was developed that robustly quantifies GCL density. In retinas from both blast-injured and control mice, greater cell densities were observed in the central compared to peripheral retina. In the peripheral retina, blast-injured mice exhibit a significant decrease in cell density compared to controls (p = 0.03, Students t-test). In the central retina, blast-injured mice exhibit a trend of reduced cell density compared to controls (not significant).

Conclusion(s): These results demonstrate that this mouse model of blast-induced TBI involves GCC-thinning and a loss of GCL cellularity at 4 months post-blast. Using this model, SD-OCT, and our semi-automated quantification technique, our ongoing studies will test mechanisms contributing to this RGC susceptibility, with a long term goal of contributing to the development of improved clinical testing and treatment of visual deficits to those suffering from TBI.
Bioinformatic Analysis Uncovers Altered Gene Expression in a Cell Culture Model of Age-related Macular Degeneration

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Age-related macular degeneration (AMD) is the leading cause of irreversible blindness among elderly adults in developed nations. As loss of blood vessels occurs concomitantly with activation of the innate immune system in eyes affected by AMD, we hypothesized that activation of the complement immune system may alter homeostatic gene expression in endothelial cells, abetting AMD pathogenesis. To test this hypothesis, we challenged primate choroidal endothelial cells with complement activators and measured differential gene expression by RNA-Seq. Bioinformatic analysis revealed that complement activation alters a wide range of genetic pathways, including robust modulation of vascular development, consistent with AMD etiology.
Automated Discovery of Optic Nerve Head Structural Features from Image and Genetic Data

Mark Christopher

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Objective: To discover novel associations between optic nerve head (ONH) structure, genetic factors, and disease by applying computational methods to analyze stereo fundus images and genotyping data.

Methods: Stereo fundus images captured from genotyped participants (n=1057) of the Ocular Hypertension Study were used to measure the structure of the ONH. A stereo correspondence algorithm, optimized for fundus images, was applied to the images, generating a 3D map of the ONH region for each participant. Principal component analysis (PCA) was applied to the maps to extract structural features. The relationships between ONH structural features and allelic state at several glaucoma-associated loci were then modeled using a linear discriminant approach to maximize the predictive power. This resulted in genotype-based ONH structural features representing an estimate of the contribution of each locus to ONH structure. The resulting features were evaluated based on the strength of their association with genotype and their utility in early prediction of glaucoma.

Results: The ONH structural features exhibiting strongest associations with genotype (p << 0.05) were identified for loci in the genes SIX1/SIX6, ATOH7, CDKN2B, TLR4, and ELOVL5. Incorporating these features into a model used for early prediction of glaucoma resulted in substantial increase in predictive power compared to a baseline model using only PCA-based ONH structural features.

Conclusion(s): The contribution of glaucoma-associated genes to ONH structure was evaluated by applying computational methods to a large dataset. By using a model that incorporated both imaging and genetic data, novel associations between phenotype and genotype were revealed. The identified ONH structural features were significantly associated with genotype and improved performance of glaucoma prediction models. Future work will examine additional genetic loci in order to further improve models used to predict and track glaucoma.
Triplication of Upstream Regulatory Sequences Leads to Gene Dysregulation in Patients with Cavitary Optic Disc Anomaly

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Background/Purpose: Cupping or excavation of the optic nerve head is a chief feature of glaucoma. A similar excavated appearance of the optic nerve is also the primary clinical sign of other congenital malformations of the eye including optic nerve head coloboma, megalopapilla, optic pit, and morning glory disc anomaly. Collectively, these congenital malformations are termed cavitary optic disc anomaly (CODA). Clinical similarities between CODA and glaucoma have suggested that these conditions may have overlapping pathophysiology. The purpose of this study is to identify and functionally characterize the gene that causes autosomal dominant CODA in a multiplex family with 17 affected members.

Methods: The gene that causes CODA was previously mapped to a 13.5 million base pair (Mb) locus on chromosome 12q14. Members of the CODA pedigree was tested for copy number variations (CNVs) in the chromosome 12q14 region with custom comparative genomic hybridization (CGH). Confirmed CNVs were analyzed for their effect on downstream genes using a pGL3 luciferase reporter gene construct in HEK293T cells. Protein expression in the adult human retina and optic nerve was assessed by immunohistochemistry.

Results: We identified a triplication of a 6,000 bp (6Kb) DNA segment upstream of matrix metalloproteinase 19 (MMP19) in all affected members of the CODA pedigree. No control subjects carried this mutation. Moreover, we detected an overlapping triplication in another small CODA pedigree. The luciferase reporter gene assay showed that the 6Kb sequence spanned by the CNV in CODA subjects functioned as a transcription enhancer, in particular, a 774 bp segment had a strong positive influence (8-fold higher) on downstream gene expression. Lastly, we detected robust and specific expression of MMP19 in optic nerve head at the site of the laminar region.

Conclusion(s): We have identified a CNV mutation in the promoter sequence of the MMP19 gene that co-segregates with CODA in our large 17 member pedigree. Moreover we have shown that the CNV spans DNA sequences that powerfully enhance downstream genes (i.e. MMP19) and that MMP19 is expressed in the optic nerve. Together these data strongly suggest that overexpression of MMP19 in the optic nerve due to triplication of an upstream enhancer element may cause CODA.

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Genetic Mapping of a Novel Disease Locus in a Canine Model of Primary Angle Closure Glaucoma

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Background/Purpose: Primary angle-closure glaucoma (PACG) is one of the most prevalent forms of glaucoma. Several dog breeds are susceptible to developing PACG, which suggests a genetic basis for the disease. We have identified a four-generation Basset Hound pedigree with characteristic autosomal recessive PACG that closely recapitulates PACG in humans. Our aim is to utilize gene mapping and whole exome sequencing approaches to identify PACG-causing sequence variants using the canine as a model organism.

Methods: Extensive clinical phenotyping of all pedigree members was conducted. 170,000 SNP markers were genotyped in 9 affected and 12 unaffected pedigree members using the Illumina CanineHD SNP Chip. Two-point and multipoint linkage analyses of genome-wide SNP data were performed using Superlink-Online SNP-1.1. Marker allele frequencies were estimated using SNP data from 10 unaffected Bassets following the exclusion of sample relatedness. To identify homozygous regions that segregate with the disease phenotype in the affected animals, homozygosity mapping was carried out using Homozygosity Mapper. Targeted exome capture was performed using the Agilent SureSelect exon kit and sequence alignment was executed on CanFam2 Ensemble and Refseq reference sequences.

Results: Using genome-wide, multipoint linkage analysis, a 1.82Mbp locus was mapped to the distal portion of chromosome 19 (Chr19:54,949,124-56,765,346) with a maximum LOD score of 3.24. The locus contains 12 predicted canine genes and is completely syntenic to a conserved human locus on chromosome 2. Investigation of haplotype phase revealed complete concordance of haploblock inheritance with the disease phenotype in all affected Bassets. Homozygosity mapping revealed sharing of a 0.49 Mbp region contained within the mapped haploblock on chromosome 19 among all affected versus unaffected animals. Using exome sequencing analysis, a total of 109 variants segregating in a recessive pattern were identified in this region. Of the disease-segregating variants, 25 were found within exons and 4 of these result in amino acid substitutions.

Conclusions: Our findings of a genetically linked locus support the segregation of an underlying genetic defect with PACG in the Basset Hound. Our results also provide evidence for a number
of potentially causative variants that segregate with PACG in the BH, which are currently the focus of our investigation. We anticipate for these studies to provide valuable insight into the genetics of human PACG by enabling the identification of genes and mechanisms that contribute to the development of disease in both canines and humans.
CEP290 Gene Addition Rescues Cilia Defect in CLA Patient Cells

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Mutations in CEP290 are the most common cause of Leber congenital amaurosis (LCA), a severe inherited retinal degenerative disease for which there is currently no cure. Autosomal recessive CEP290-associated LCA is a good candidate for gene replacement therapy, and cells derived from affected individuals give researchers the ability to study human disease and therapeutic gene correction in vitro. Here we report the development of lentiviral vectors carrying full-length CEP290 for the purpose of correcting the CEP290 disease-specific phenotype in human cells. A lentiviral vector containing CMV-driven human full-length CEP290 was constructed. Following transduction of patient-specific, iPSC-derived, photoreceptor precursor cells, reverse transcriptase-PCR analysis and western blotting revealed vector-derived expression. As CEP290 is important in ciliogenesis, the ability of fibroblast cultures from CEP290-associated LCA patients to form cilia was investigated. In cultures derived from these patients, fewer cells formed cilia compared with unaffected controls. Cilia that were formed were shorter in patient-derived cells than in cells from unaffected individuals. Importantly, lentiviral delivery of CEP290 rescued the ciliogenesis defect. The successful construction and viral transfer of full-length CEP290 brings us closer to the goal of providing gene- and cell-based therapies for patients affected with this common form of LCA.