Resident and Fellow Research Day 2020
Department of Ophthalmology and Visual Sciences, University of Iowa

Session I - Paper 1

Ocular Surface Flora Changes Prior to Cataract Surgery With and Without Pre-operative Antibiotics

Caroline W. Wilson, MD

Primary supervisors: Jaclyn Haugsdal, MD, Thomas Oetting, MD
Coauthor: Daniel Terveen, MD

Purpose: To investigate how the pre-operative use of topical moxifloxacin prior to cataract surgery affects the ocular surface flora and to determine if its use selects for resistant strains of ocular surface flora.

Methods: Conjunctival culture swabs were obtained at the pre-operative visit prior to cataract surgery and again the morning of cataract surgery in 17 patients who used topical moxifloxacin prior to surgery and in 11 control patients who did not use moxifloxacin prior to surgery. In the 17 patients who were prescribed topical moxifloxacin, they were instructed to use the medication four times daily for three days before surgery. Cultures results from the study and control groups were analyzed for bacterial species growth and resistance patterns, determined by MALDI-TOF and antibiotic sensitivity analysis.

Results: In the 17 patients who used topical moxifloxacin prior to cataract surgery, 9 of 17 (52%) had persistent ocular surface bacterial growth. All of the control patients had persistent bacterial growth ($p = 0.0097$). Bacterial resistance to moxifloxacin developed in 3 of 17 (17.6%) patients using moxifloxacin; no resistance to moxifloxacin developed in the control patients ($p = 0.2579$). Coagulase-negative staphylococci were the most commonly cultured bacterial species in both groups, with *Staphylococcus epidermidis* growing in 86% of all cultures (82% in the moxifloxacin group and 91% in the control group). The other most common bacterial species in both groups were corynebacterial species (32%) and *Staphylococcus aureus* (21%).

Conclusions: Use of topical moxifloxacin prior to cataract surgery does not reduce ocular surface flora effectively in most patients. Further, it may select for resistant strains of ocular surface flora that could potentially lead to the reduced efficacy of intracameral moxifloxacin against pathogenic bacteria at the time of cataract surgery.

Resident and Fellow Research Day 2020
Department of Ophthalmology and Visual Sciences, University of Iowa

Session I - Paper 2

The Effect of Transcranial Direct-Current Stimulation on Microsurgical Simulation Performance

Anthony Chung, MD

Primary Supervisors: Erin M. Shriver M.D. FACS, Elliott H. Sohn M.D.
Co-authors: Charlene Tran B.S., Benjamin Walker B.S., Kai Wang Ph.D.

Background and Purpose: Transcranial direct current stimulation (tDCS) has been shown to improve skill acquisition, retention, and performance of various tasks when applied to the primary motor cortex, such as finger pinch tasks, lower extremity balancing tasks, and Olympic ski jumping. Evidence suggests tDCS strengthens synapses by lowering neuronal membrane potentials, recruiting neurons, and promoting synergistic firing of action potentials. The purpose of this study is to evaluate the effect of tDCS on microsurgical skill acquisition as measured on the Eyesi ophthalmic surgical simulator.

Methods: Undergraduate, physician assistant, and medical students from the University of Iowa were invited to participate in this randomized double-masked prospective study. Medically eligible participants completed a questionnaire examining demographic information and their history of video games, musical instruments, and other activities. Participants were then randomized to either tDCS or control (sham). Both the tDCS and sham stimulation were provided by Halo Neurostimulation System; a product developed by Halo Neuroscience (San Francisco, CA). Participants in the tDCS group received sustained stimulation at 2 mA for 20 minutes in a single, continuous session. Those in the control group received sham stimulation via a gradual increase in current over 30 seconds immediately followed by a gradual decrease in current over 30 seconds without a period of sustained stimulation. All participants wore the headset throughout the training sessions to avoid revealing randomization. Baseline evaluation was measured on Eyesi Level 2 anterior segment navigation, anterior segment bimanual training, and posterior segment navigation tasks. Participants then trained on each task for 10 minutes and completed a final evaluation on each task. This testing protocol was repeated for 2 additional sessions on separate days.

Results: Forty-five participants were enrolled and had complete baseline data. At completion, 37 participants had complete data for the anterior segment navigation and bimanual tasks and 36 participants for the posterior navigation task. On baseline evaluation, women had greater total scores than men on anterior navigation (11.0 vs 1.0; $p = 0.019$). Medical students had greater total scores (33.9 vs 15.0, $p = 0.006$) and shorter trial times (164.6 vs 218.0 seconds, $p = 0.044$) than undergraduates on the bimanual task. The stimulation and control groups differed at baseline in total scores for the bimanual task (36.3 vs 11.5, $p < 0.001$). Hand dominance and past fine motor activities showed no difference at baseline in any of the three tasks. Both the stimulation and control participants had greater final scores and faster trial times in all 3 tasks at the end of the study relative to their baseline evaluation. The stimulation group had greater total scores (69.5 vs 54.0, $p = 0.008$) and faster trial times (47.7 vs 57.7, $p = 0.028$) on the posterior segment navigation task. There were no statistically significant differences in total scores between the stimulation and control groups for anterior segment tasks.

Conclusions: Medical students outperformed undergraduates and women outperformed men at baseline. All participants showed improvement in total scores and trial times in all Eyesi tasks. Neural stimulation can potentially augment posterior segment surgical skill acquisition.

Resident and Fellow Research Day 2020
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Session I - Paper 3

Fibrous Downgrowth Among First-Time Corneal Transplant Recipients

David Ramirez, MD

Primary supervisor: Mark A. Greiner, MD
Co-authors: Lai Jiang, MD, Christopher Fortenbach, MD PhD, Kendra Frey, BS

Background and Purpose: To describe the demographic and historical factors among patients with a first-time diagnosis of fibrous downgrowth (FD), a risk factor for corneal decompensation, at the University of Iowa.

Methods: Medical records for all keratoplasty patients with a histopathological diagnosis of fibrous downgrowth between 1/1/2002 and 7/17/2019 were reviewed retrospectively, and only first-time keratoplasty recipients were included. We excluded outside globe submissions and patients with a diagnosis of fibrous downgrowth on non-primary transplants. We recorded past ocular history, with particular attention to prior ocular surgeries; indication for primary keratoplasty, and duration of graft survival.

Results: 79 eyes from 77 patients (35% female, mean age 60.7 years) with a diagnosis of fibrous downgrowth after initial keratoplasty procedure were included for analysis. Of these, 82.2% had a history of corneal disease, 41.7% had a history of glaucoma, 39.2% had retinal disease, 19.0% had a history of ocular trauma, and 15.1% had uveitis. Additionally, 72 eyes (91.1%) underwent surgery prior to initial keratoplasty, including cataract surgery (75.9%), retinal surgery (40.5%), and glaucoma surgery (27.8%). Keratoplasty was indicated most commonly for aphakic bullous keratopathy (34.1%), infection (19.0%), and pseudophakic bullous keratopathy (16.5%). The most common keratoplasty technique performed was penetrating keratoplasty (59.5%), followed by Descemet stripping automated endothelial keratoplasty (DSAEK; 31.6%). The mean graft survival was 2.8 years (range 0.9-7.7 years).

Conclusions: Nearly half of patients had a history of glaucoma and retinal disease, with a similar percentage undergoing glaucoma surgery or retinal surgery prior to first keratoplasty. This may suggest incisional surgery may impact patients' risk of developing fibrous downgrowth. Further investigation should focus on the effect of this diagnosis on graft survival and the risk of regrafting.

Resident and Fellow Research Day 2020
Department of Ophthalmology and Visual Sciences, University of Iowa

Session I - Paper 4

Ocular Cicatricial Pemphigoid: Late Presentations and Systemic Involvement at a Single-Center Academic Practice

Lai (Larry) Jiang, MD

Primary supervisor: Mark A. Greiner, MD
Co-author: Caroline Wilson, MD

Purpose: Ocular cicatricial pemphigoid (OCP) is a rare subset of mucous membrane pemphigoid that results in progressive, visually debilitating disease. In many patients, OCP is recognized late in the disease course once clinical signs are advanced. Clinical diagnosis of OCP is supported by conjunctival or other mucosal biopsy, which is not always conclusive. This study sought to identify clinical factors that may assist with earlier diagnosis of OCP.

Methods: Charts of all patients in the Epic database with biopsy- or clinically- proven OCP were reviewed for demographics, ocular history, exam findings including Foster staging, extraocular mucosal involvement, and outcomes.

Results: 34 patients were included in the study. All patients were Caucasians aged 41-93 years (53% female, 47% smokers). Twenty-nine (85%) patients had positive mucosal biopsies. Positive conjunctival biopsies were present in 65%. Of 20 patients with review of systems querying extraocular mucosal involvement, 19 had systemic symptoms (85% oral). Histories of trichiasis (53%), cicatricial entropion (24%), and eyelash or eyelid procedures (41%) were common prior to presentation. 52% had a history at least one extraocular procedure prior to presentation. Foster stage was 3 or worse in 75% at presentation. One-third of patients showed clinical progression while on treatment. 71% of eyes without ocular involvement at presentation developed ocular findings. 47 eyes (70%) required lash procedures. Mean initial and final logMAR BCVA were 0.318 (IQR 0-0.40) and 0.485 (IQR 0.1-0.38), respectively ($p=0.014$).

Conclusions: Most OCP patients in our study presented late in disease with poor visual outcomes. One third of patients had disease progression despite treatment. Majority of the eyes with no ocular findings developed ocular involvement and most patients required procedures to treat disease related complications. Clinical factors associated with OCP at presentation included positive systemic mucosal involvement, especially oral, and a strong history of eyelash and eyelid pathology. Given the low sensitivity of conjunctival biopsy, clinical history - including review of systems focused on extraocular mucosal symptoms - may be paramount to identifying affected patients early. Further studies are needed to determine if earlier diagnosis and treatment would improve patient outcomes.

Resident and Fellow Research Day 2020
Department of Ophthalmology and Visual Sciences, University of Iowa

Session I - Paper 5

Metabolic and Proteomic Indications of Diabetes Progression in Human Aqueous Humor

Christopher R. Fortenbach, MD, PhD

Supervisor: Mark Greiner, MD
Co-Authors: Jessica M. Skeie; Darryl Nashimura

Background and Purpose: Diabetes mellitus poses a significant threat to ocular health and vision. While the retina is widely recognized as a target of damage, diabetes also impacts the anterior segment and may result in diabetic patients requiring more frequent corneal and glaucoma surgeries. We hypothesize that the systemic metabolic and proteomic derangement observed in the progression of diabetes also influences the composition of the aqueous humor (AH), which ultimately impacts anterior segment health. In order to identify the changes associated with diabetes progression, we mapped the metabolite and proteomic profiles of AH samples of patients with varying severity of type II diabetes (T2DM).

Methods: Patients were classified as nondiabetic (control), non-insulin-dependent diabetic without advanced features of disease (NAD-ni), insulin-dependent diabetic without advanced features (NAD-i), or diabetic with advanced features (AD). AH samples were collected during anterior segment surgeries and frozen immediately. Metabolites were identified by GC-MS (Thermo Q Exactive GC). Data were collected in the full mass range (50-700 Da) and identification of metabolites was based on comparison with in-house standards and their retention times using Tracefinder 4.1 (Thermo Fisher). Proteins were identified by UHPLC-MS/MS (Thermo Fisher Scientific Easy-nLC 1000 UHPLC system) and peptides were identified using protein sequence libraries available from UniProtKB, X!Tandem, and OMSSA. Pathway and statistical analyses were conducted using Partek Genomics Suite, MetaboAnalyst 4.0, and Ingenuity Pathway Analysis (IPA; Qiagen).

Results: A total of 12 control, 15 NAD-ni, 3 NAD-i, and 12 AD samples were included for analysis. AH samples from diabetic patients across severities demonstrated differences in various metabolites compared to control patients. Elevated levels of several carbohydrates including glucose and fructose were detected at all diabetic severities. Other metabolites, such as lysine, alanine, and malate were elevated relative to controls only in AD samples. These findings were mirrored in metabolic and proteomic pathway analyses, which showed altered carbohydrate and glutathione metabolism among all diabetic groups while amino acid biosynthesis changes were impacted by diabetes severity.

Conclusions: Diabetes results in metabolic and proteomic perturbations detectable in the AH, and unique changes in substrate metabolism become manifest as T2DM severity worsens. Changes in AH composition may serve as an indicator of disease severity and risk assessment of anterior segment cells and structures.

Session II – Paper 6

Responding to Patient-Initiated Verbal Sexual Harassment: Outcomes of a Novel Workshop for Trainees and Faculty

Lauren E. Hock, MD

Primary Supervisor: Erin M. Shriver, MD
Co-Authors: Patrick B. Barlow, PhD; Brittni A. Scruggs, MD, PhD; Thomas A. Oetting, MD, MS; Denise A. Martinez, MD; Michael D. Abràmoff, MD, PhD

Background and Purpose: Patients are the most common source of gender-based harassment of resident physicians, yet residents receive little training on how to handle patient-initiated harassment. Existing models train faculty to intervene toward harassment of medical trainees, but few resources exist for residents who wish to address patient-initiated verbal sexual harassment themselves. The purpose of this study was to assess the effect of a novel workshop on tools for responding to patient-initiated verbal sexual harassment on resident and faculty preparedness to respond to patient-initiated harassment.

Methods: A 50-minute workshop was developed, taught, and evaluated to prepare residents and faculty to respond to patient-initiated verbal sexual harassment toward themselves and others. The workshop used an interactive lecture and role play scenarios to teach a toolkit of communication strategies for responding to harassment from patients. Ninety-one participants (57 trainees, 34 faculty) completed retrospective pretest-posttest surveys at 1 of 5 sessions.

Results: Before the workshop, two-thirds (67.0%) of physicians had experienced patient-initiated sexual harassment and less than one-third (31.8%) had ever addressed it. Seventy-five percent of participants had never received training on responding to sexual harassment initiated by patients. After the workshop, participants reported significant improvement in their preparedness to recognize and respond to all forms of patient-initiated verbal sexual harassment ($p<0.001$), with the greatest improvements noted in responding to mild forms of verbal sexual harassment, such as comments on appearance, attractiveness, or inappropriate jokes ($p<0.001$).

Conclusions: This workshop fills an important void as it prepares residents and faculty to respond to instances of verbal sexual harassment from patients that are not directly observed. Use of role play and rehearsal of an individualized response script significantly improved participants' preparedness to respond to harassment toward themselves and others.

Session II – Paper 7

Impact of Educational Campaign on Identification and Referral of Women with Orbital Fractures and Rupture Globes Secondary to Intimate Partner Violence

Salma Dawoud, MD

Supervising author: Erin M. Shriver, MD, FACS
Co-authors: Bridget Zimmerman, PhD; Ali Cohen, MD; Thomas J. Clark, MD; Keith D. Carter MD, FACS

Purpose: To determine rates of intimate partner violence (IPV)-related ruptured globes, orbital floor and ZMC fractures, and referral to ancillary services in women after an educational campaign regarding IPV injury patterns and screening. Previous studies indicate significant gaps in identifying mechanisms of injury and involvement of ancillary services for identified IPV patients.

Methods: A retrospective review was performed of female patients who sustained open globes, orbital floor fractures, or ZMC fractures between January 2015 and February 2019. Statistical analyses were performed on pre- and post- educational campaign data using Pearson Chi-square test and Fisher's exact test.

Results: A total of 216 women with orbital fractures were identified with orbital floor fractures accounting for 81.5% (176/216) and ZMC fractures accounting for 18.5% (40/216). A mechanism of injury was documented in every case and leading mechanisms were falls (53.5%, 118/216), motor vehicle accidents (15.9%, 33/216), non-IPV assault (13.4%, 29/216), IPV assault (10.2%, 22/216), and accident by inanimate object (3.2%, 7/216). The rate of documented IPV-related orbital fractures was stable when compared to pre-educational campaign rates (difference 3.5%, p=0.28). ZMC fractures accounted for 36.4% (8/22) of IPV-assault injuries compared to 17.2% (5/29) in the non-IPV assault group. Social work referrals for IPV-related orbital fractures increased to 90.9% (20/22) when compared to pre-educational campaign rates (difference 56%, p<0.0001). Similarly, home-going safety assessments increased to 81.8% (18/22) (difference 79%, p<0.0001) and law enforcement involvement increased to 72.3% (16/22) (difference 50%, p=0.0003). A total of 51 women with open globes were identified. The most common injuries were ruptured globe (78.4%, 40/51), corneoscleral laceration (9.8%, 5/51), corneal laceration (7.8%, 4/51), and scleral laceration (3.9%, 2/51). The leading documented mechanism of injury was falls (58.8% 30/51). IPV assault (9.8%, 5/51), non-IPV assault (9.8% 5/51), and accident by inanimate object (9.8% 5/51) were the next most common mechanisms followed by animal-related injuries (3/51, 5.8%). All IPV patients sustained ruptured globes. The rate of documented IPV-related ruptured globes trended towards but was not significant compared to rates before the educational campaign (difference of 6.3%, p =0.08). In the 5 patients with ruptured globes secondary to IPV assault, social work involvement, law enforcement involvement, and home going safety assessments were documented in 5, 4, and 4 patients respectively. Previous analysis prior to the educational campaign revealed documentation in 4, 2, and 3 patients respectively in the 5 patients with IPV-related ruptured globes. No significance was noted in this small sample size.

Conclusion: Despite declining rates of IPV in Iowa since 2010, documented IPV-related orbital fracture rates and globe rupture rates remained stable to slightly increased after the educational campaign. After the initiative, assessment of home going safety and involvement of social work and law enforcement increased significantly in IPV-related orbital fractures. Injuries secondary to IPV are more severe, as evidenced by ZMC fractures being twice as common in IPV assault when compared to non-IPV assault. Targeted screening of women with orbital fractures and open globes is essential for the detection and referral of IPV patients.

Resident and Fellow Research Day 2020
Department of Ophthalmology and Visual Sciences, University of Iowa

Session II – Paper 8

Visual Outcomes in the Management of Orbital Compartment Syndrome

Austin R. Fox, MD

Primary supervisor: Erin M. Shriver, MD, FACS
Co-author: Andrew C. Lin, MD

Background and Purpose: Orbital compartment syndrome (OCS) is a vision-threatening emergency in which an elevated intraorbital pressure results in decreased perfusion of the optic nerve and retina. OCS is a clinical diagnosis, and rapid diagnosis and management of OCS are necessary to prevent ischemia and permanent vision loss. Based on animal studies, it has been recommended that LCC be performed within 100 minutes from onset of OCS. However few studies have evaluated factors affecting visual outcomes, including the time from OCS onset to intervention. The purpose of this study is to describe the largest reported cohort of patients with OCS and to evaluate factors affecting the visual outcome of these OCS patients.

Methods: A retrospective review was performed to identify patients diagnosed with orbital compartment syndrome who underwent emergency lateral cantholysis/canthotomy (LCC) over a 29-year period between December 1989 to December 2018 at UIHC. The time to surgical intervention ('Time to LCC'), age, sex, presence of relative afferent pupillary defect (RAPD), mechanism of injury, visual acuity (VA) at presentation and at final follow-up, intra-ocular pressure (IOP) at presentation and at final follow-up, eye laterality, associated injuries, incipient causes, and the primary service performing the LCC were recorded. Complete case analysis was used, and patients with missing data including initial and final visual acuity or intraocular pressure were excluded from the analysis. Statistical significance of continuous and categorical variables was calculated by a one-tailed Mann-Whitney U test and Fisher's Exact test, respectively.

Results: Fifty-three subjects were identified as having undergone LCC for OCS, and 31 subjects met inclusion criteria. The mean initial IOP was 61.5 ± 17.7mmHg, and the mean final IOP was 27.5 ± 12.6 mmHg. Only 3 (9.7%) patients underwent LCC in under 100 min, with a mean time to LCC of 277.7 ± 144.6 min (range: 10.0 - 600.0 min). Upon presentation, 23 (74.2%) had visual acuity worse than 20/200, 7 (22.6%) between 20/50 and 20/200, and 1 (3.2%) 20/40 or better. At final follow-up, 13 (41.9%) had a VA worse than 20/200, 8 (25.8%) had a VA between 20/50 and 20/200, and 10 (32.3%) patients 20/40 or better vision. Nineteen (61.3%) participants had improved VA, 9 (29.0%) remained the same, and 3 (9.7%) worsened. Time to LCC and age were associated with the degree of visual recovery ($p = 0.02$ and $p = 0.001$, respectively)

Conclusions: Decreased time to intervention with LCC and younger age are both associated with a more favorable final visual outcomes in the management of OCS. Of the 28 participants who received LCC after 100 minutes: 17 improved, 8 remained the same, and 3 worsened, and the longest time delay to LCC in which the patient's visual acuity improved was 600 minutes. LCC should be performed without delay to maximize the possibility of visual recovery regardless of the elapsed time from the onset of OCS.

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Session II – Paper 9

Markers for Sebaceous Carcinoma: Enhancing Histologic Analysis

Brittany Simmons, MD

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Co-author: Keith Carter, MD

Background and Purpose: Sebaceous carcinoma is a potentially life-threatening condition that often masquerades as benign disease. Biopsy is required for correct diagnosis; however, the heterogeneity of the disease and lack of a definitive immunohistologic marker can make diagnosing sebaceous carcinoma difficult. Treatment typically relies on complete excision, which is complicated by the often multifocal and subclinical intraepithelial spread of the disease. The primary purpose of this study is to identify reliable histologic markers for sebaceous carcinoma of the periocular region. Secondarily, the investigators aim to use these markers to visually label diseased tissue in fresh specimens and, ultimately, in a patient prior to biopsy to aid in visualizing tumor at the time of excision. Having this capability would potentially reduce intraoperative excision time and the need for serial excisons. A tumor marker that can be evaluated in both fresh and fixed tissue samples would be ideal. Elsewhere in the body, cell surface markers like transmembrane mucins and carbohydrates have been used to identify cancer, monitor response to treatment, and surveil for progression of disease. The eyelid and ocular surface exhibit numerous mucin-derived markers, and these can be dysregulated in ocular surface and even systemic disease. Lectins are carbohydrate-binding proteins that are ubiquitous and involved in cell adhesion, glycoprotein synthesis, and signaling by acting as cell surface receptors, regulating inflammatory reactions, and modulating autoimmune processes. Altered cell surface glycoconjugates have previously been implicated in ocular disease, resulting in distinctive lectin and carbohydrate expression in drusen, choroidal neovascularization, and birdshot chorioretinopathy. Although there are no comprehensive studies evaluating the presence of lectin-binding molecules in the normal eyelid or in sebaceous carcinoma of any location, the authors believe that ocular surface markers recognized by lectins are likely present in normal eyelid tissue and may be dysregulated in – and thus useful as markers of – sebaceous carcinoma.

Methods: IRB approval was secured. Previously obtained paraffin-embedded samples of control eyelid and eyelid with sebaceous carcinoma were collected. Histochemistry with the Ulex europaeus agglutinate (UEA) and wheat germ agglutinate (WGA) lectins was performed on 6 sections of normal eyelid tissue controls from 2 patients. Fluorescently labeled specimens were examined with confocal microscopy. Evaluation of sebaceous carcinoma specimens is in process.

Results: In normal controls, UEA binding was observed in epidermal and vascular tissue. WGA binding was observed diffusely, including cell membranes and extracellular matrix.

Conclusions: Lectin histochemistry is a viable approach for identifying cell surface markers in eyelid tissue. There is differential expression of glycoconjugates in these tissues. Future directions include expanding the number of normal eyelid specimens tested, exploring a wider array of lectin binding, and evaluating lectin histochemistry in sebaceous carcinoma samples. A battery of lectin testing in both normal eyelid and confirmed periocular sebaceous carcinoma biopsies may ultimately identify molecular markers unique to sebaceous carcinoma.

Resident and Fellow Research Day 2020
Department of Ophthalmology and Visual Sciences, University of Iowa

Session II – Paper 10

Evolutionary Dynamics of Retinoblastoma Progression

Matthew G. Field, MD, PhD

Primary supervisor: J. William Harbour, MD
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Background and Purpose: Retinoblastoma (Rb) is an aggressive childhood eye cancer and one of the most important causes of childhood cancer death worldwide. Biallelic inactivation of the *RB1* tumor suppressor in a susceptible retinal progenitor cell is the initiating event in most Rbs, leading to differentiation failure and uncontrolled proliferation. Despite this shared genetic origin, Rbs vary widely in their clinical and histopathologic severity, and this is not fully explained by the nature of the *RB1* mutation. The purpose of this study was to identify clonal and subclonal driver mutations and copy number gains and losses in Rb tumors, as well as the order of their occurrences, to better understand how evolutionary mechanisms drive Rb progression.

Methods: Twenty-three Rb tumor and matched germline samples underwent exome sequencing to determine copy number gains and losses and driver mutations. Two matched Rb vitreal seed samples were analyzed to assess for evolutionary progression from the primary tumor to the seed. For each sample analyzed, mutations and copy number gains and losses were assigned to clonal and subclonal clusters and mapped to phylogenetic evolutionary trees.

Results: All Rb samples analyzed were found to have biallelic loss of *RB1*. Most commonly a germline or somatic mutation occurred on one *RB1* allele with either a loss of heterozygosity event that included the other allele or an isodisomy event resulting in duplication of the mutated allele. In some samples, regions of chromosome 13 that contained *RB1* showed evidence of chromotripsis, chromosomal shattering, or deep deletion. By the time of enucleation, these two events had predominantly occurred in 100% of tumor cells. The second most commonly occurring mutation was in *BCOR*, which was also a double hit, loss-of-function mutation. Copy number gains and losses were enriched for 1q, 2p, and 6p gain and 16p and 16q loss. The number of clonal and subclonal clusters was positively correlated with date of enucleation, meaning that older patients tended to have more complex evolutionary patterns. Vitreal seeds showed development of independent clusters from the primary, including the development of additional mutations and copy number gains and losses, providing evidence of ongoing evolutionary fitness that may explain how seeds acquire the ability to survive in hypoxia and overcome anoikis-induced apoptosis.

Conclusions: Most tumors, regardless of age, had the most common copy number gains and losses and driver mutations, including *RB1* in 100% of tumor cells. Tumors that developed at an early age had fewer tumor clusters and mutations, whereas tumors diagnosed at a later age tended to have more clusters, more mutations, and more complex evolutionary patterns. Most interestingly, vitreal seeds were found to have independent subclones from the primary tumor, providing evidence of ongoing tumor evolution. This ongoing evolution may explain how the seeds acquire the ability to survive in hypoxia, develop resistance to conventional therapies, and survive in an anchorage-independent manner. Findings in this study provide improved understanding of Rb progression and offer additional therapeutic targets for this deadly cancer.

Resident and Fellow Research Day 2020
Department of Ophthalmology and Visual Sciences, University of Iowa

Session II – Paper 11

Outcomes Following Brachytherapy for Uveal Melanoma: The UIHC Experience

Benjamin L. King, MD

Primary Supervisors: Elaine Binkley, MD; H. Culver Boldt, MD
Co-authors: Sarah Bell, Mohammed Milhem, MD

Background and Purpose: Uveal melanoma (UM) is the most common primary intraocular malignancy in adults. While plaque brachytherapy has become the preferred treatment modality in many cases, local recurrence remains a significant risk and can result in increased ocular morbidity and greater risk for metastasis. The use of intra-operative ultrasound has been shown to decrease the incidence of local tumor recurrence. The use of peri-operative ultrasound to detect tissue edema or hemorrhage that shifts the tumor out of the prescribed dose range, and to adjust the prescribed treatment dose accordingly is not widely used at many centers. We conducted a retrospective investigation of patients treated at this institution for UM to quantify treatment success with brachytherapy using intraoperative and perioperative ultrasound to monitor plaque centration and apposition during treatment.

Methods: Electronic health records for consecutive patients with UM undergoing primary treatment with Iodine-125 brachytherapy at the University of Iowa between 2008 and 2019 for whom both intra-operative and peri-operative ultrasound were utilized were retrospectively reviewed. B-scan ultrasonography was performed intraoperatively to confirm plaque centration and then repeated prior to removal to confirm the prescription height relative to the tumor apex during treatment. Brachytherapy was extended accordingly if the tumor apex was displaced outside the prescription height. Patients were recommended follow up at 6 month intervals for the first five years following treatment, and annually thereafter. Local tumor control and metastasis data were recorded for each patient. Kaplan-Meier analysis was used to quantify the incidence of local recurrence, metastasis and mortality.

Results: 372 patients with uveal melanoma underwent plaque brachytherapy between 2008 and 2019. Perioperative adjustment of prescription height was required in 7.8% (n=29) and the plaque was re-positioned in 0.8% (n=3). Local recurrence was diagnosed in 0.8% (n=3). Kaplan-Meier estimate of local control was 97% (95% CI 94%-99%) at both 5 and 10 years and no patient who required plaque revision or prescription height adjustment developed local recurrence. Metastasis-free survival was 86% (81%-90%) and 75% (66%-82%) at 5 and 10 years respectively. Overall survival was 84% (79%-88%) at 5 years and 59% (45%-70%) at 10 years.

Conclusions: In this large single-center retrospective case series, ultrasound-guided plaque brachytherapy achieved local control in almost all patients with substantially lower rates of local recurrence compared with historical data. It is unknown whether decreased incidence of local recurrence has a corresponding decrease in the risk for metastatic disease. Further investigation is necessary to demonstrate this prospectively.

Session III = Paper 12

Progressive Neurodegeneration in Macular Telangiectasia Type 2 (MacTel)

Alec L. Amram, MD

Primary supervisor: Elliott Sohn, MD
Co-authors: Cheryl Wang, Scott Whitmore, Christine Clavell, Lance Lyons, Alex Rusakevich, Ian Han, James Folk, Culver Boldt, Karen Gehrs, Edwin Stone, Stephen Russell, Kyungmoo Lee, Michael Abramoff, Charles Wykoff

Purpose: MacTel has a complex pathogenesis that involves the retinal vasculature with a significant neurodegenerative component. In addition to outer retinal abnormalities (e.g. ellipsoid zone) that correlate with visual dysfunction, patients with MacTel have been shown to have retinal ganglion cell layer (GCL) and nerve fiber layer (NFL) thinning, but the rate of thinning of retinal layers is unclear. We sought to quantify the change in thickness over time of retinal layers in patients with non-proliferative MacTel.

Methods: This is an IRB-approved retrospective study of patients with MacTel presenting to the University of Iowa and Retina Consultants of Houston with at least two Heidelberg Spectralis SD-OCT scans separated by over 9 months. Exclusion criteria included: glaucoma, history of optic nerve disease, proliferative diabetic retinopathy, diabetic macular edema, choroidal neovascularization from any cause, vascular occlusion, prior plaque radiotherapy, anti-VEGF therapy, or advanced age-related macular degeneration. OCTs were segmented using the Iowa Reference Algorithms (ver. 5.0.0). Mean thickness in the NFL and GCL was computed for subfield 4 of the ETDRS grid and across the total area of the ETDRS circle. Mixed effects models were fit to each layer and region. Percent change was calculated as the rate of change / baseline thickness. The NFL and GCL were analyzed globally and in ETDRS region 4.

Results: 116 patients met criteria for this study. Neither diabetes nor treatment with CAIs substantively changed thickness at baseline. We observed a rate of thinning in the NFL in subfield 4 that was measurably greater than zero (-0.26±0.09 μm/year; P = 0.003). In subfield 4 of the GCL, the rate of thinning observed in eyes treated with CAI (1.28±0.26 μm/year) was measurably faster than in untreated eyes (-0.20±0.16; P <0.001). Diabetes did not measurably alter rate of thinning compared to non-diabetic patients.

Conclusions: Patients with non-proliferative MacTel sustain progressive neurodegeneration over time that is similar to those with diabetes and no clinical retinopathy. Ongoing analyses will more definitively delineate the relationship between MacTel and neuroretinal thinning.

Resident and Fellow Research Day 2020
Department of Ophthalmology and Visual Sciences, University of Iowa

Session III – Paper 13

How to Diagnose Optic Neuropathy in a Blink!

Nitsan Duvdevan-Strier, MD

Primary supervisor: Randy Kardon MD, PhD
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Background and Purpose: In response to a light stimulus, a reflex orbicularis contraction of the upper and lower eyelid occurs, similar to the pupil light reflex. Our purpose was to determine if the eyelid light reflex can be used as an objective clinical measure of afferent visual pathology, in a similar manner to Relative Afferent Pupillary Defect (RAPD). This would be useful in patients with damaged iris or in patients whose pupils are already dilated pharmacologically. We compared the orbicularis and pupillary responses to increasing light stimuli in subjects with and without unilateral optic neuropathy (ON). We hypothesized that the orbicularis contraction correlates with pupil contraction for the same light stimulus and would produce a Relative Afferent Eyelid Defect (RAED) in eyes with optic neuropathy.

Methods: We conducted a case-control study to compare the eyelid response to light in 31 normal subjects and in 18 patients with unilateral ON. Eyelid and pupil responses to a 1 Hz, 5 second duration Ganzfeld light stimulus, increasing in intensity, were video recorded in each eye, using a hand-held ERG device (RETeval©, LKC Technologies, Gaithersburg, USA). Video frames were analyzed to assess percent change of palpebral fissure and pupil compared to pre-stimulus baseline. Inter-eye response asymmetry was quantified for the eyelid and pupil.

Results: In all subjects, the eyelid response increased as a function of light intensity. This response was significantly decreased in eyes with optic neuropathy (ON) compared to the fellow, unaffected eyes (Wilcoxon test $P<0.0001$). In the healthy subjects, there was no difference between the eyelid response to light stimuli given to the right and left eye (Wilcoxon test, $p=0.547$). The eyelid response asymmetry in ON subjects correlated with the pupil response asymmetry ($r=0.76$, $P=0.0002$, 95% CI 0.45 to 0.91).

Conclusions: Patients with unilateral optic neuropathy display a relative afferent eyelid defect (RAED) in addition to the relative afferent pupil defect (RAPD). The eyelid response correlated with the pupil response and provides a novel, additional method for evaluating optic neuropathies, even after pupil dilation.

Resident and Fellow Research Day 2020
Department of Ophthalmology and Visual Sciences, University of Iowa

Session III – Paper 14

Clinical Features and Course of Eyes with Large Disc Area and Megalopapilla

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Background and Purpose: Progressive enlargement of the cup-to-disc ratio is the most definitive criteria for diagnosis of glaucoma and is also among the strongest evidence of worsening disease. Consequently, large cup-to-disc ratios are suspicious for glaucoma. When an individual's cup-to-disc ratio is above an extreme (i.e. larger than 97.5% of a normal population), there is a high likelihood for glaucoma. However, the cup-to-disc ratio is only an accurate gauge of glaucoma in individuals with an average optic disc area. Large optic discs such as megalopapilla, optic disc areas greater than 2.5 mm^2, may appear like glaucoma due to a large cup-to-disc ratio. Our goal was to study the presenting characteristics and the frequency of progressive features of glaucoma in a cohort of patients with large disc area and megalopapilla.

Methods: Individuals with optic disc areas greater than 2.0 mm^2 and follow up greater than one year were identified via a retrospective chart review of patients visiting the Glaucoma Service at the University of Iowa.

Results: A total of 62 eyes met criteria for large disc area (LDA) and 33 for megalopapilla (MP). Average length of follow up was 7.64 years with an average of 11.46 glaucoma service appointments per eye. The age of presentation was 44.6 and 49.75 years for LDA and MP eyes respectively. The LDA group was composed of 45% males and 89% were white. The most common diagnosis in this group was glaucoma suspect (37%) followed by primary open angle glaucoma (23%). The MP group consisted of 64% males, of which 52% were white and 48% were black. The most common diagnosis was primary open angle glaucoma (49%) followed by glaucoma suspect (33%). On average, visual field mean deviation (MD) in LDA group was -0.46 dB at baseline and -0.99 dB at last follow up, and pattern standard deviation (PSD) was 1.66 dB at baseline and 3.11 dB at last follow up. In megalopapilla eyes, the baseline MD was -8.12 dB and -9.31 dB at last follow up, and the baseline PSD was 9.30 dB and 10.81 dB at their last visit. Average retinal fiber layer (RNFL) thickness in LDA group was 88 μm at baseline and 79.7 μm at last follow up. Megalopapilla eyes had an average RNFL thickness of 82.33 at baseline and 82.50 at last follow up.

Conclusions: Large optic discs and megalopapilla are often grouped as glaucoma suspects based on large cup-to-disc-ratio. However, in some situations these can be glaucoma suspect masquerades that do not have progressive enlargement of the cup-to-disc ratio or worsening visual fields over time.

Session III – Paper 15

Long-Term Follow-Up of Normal Tension Glaucoma Patients with TBK1 Gene Mutation in One Large Pedigree

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Purpose: To characterize features of glaucoma associated with a TANK binding kinase 1 (TBK1) gene duplication, which is among the most common molecularly defined causes of normal tension glaucoma (NTG).

Methods: Retrospective observational case series METHODS: We conducted a retrospective case series, by reviewing medical records of 7 members of a pedigree with normal tension glaucoma (NTG) caused by TBK1 gene duplications. Clinical features of these patients at diagnosis, throughout management, and at latest follow up were identified including age, intraocular pressure (IOP), central corneal thickness (CCT), optic nerve head appearance, and mean deviation (MD) assessed with Humphrey visual field (HVF) testing protocols.

Results: At initial diagnosis, the mean age was 35 ± 7 years, IOP was 16 ± 2.1 mm Hg, cup-to-disc (C/D) ratio was 0.9 ± 0.08, and MD assessed via HVF 30-2 and/or 24-2 testing protocols was -9.0 ± 8.9 (range: -1.8 to -27) dB in the 14 study eyes. At initial diagnosis, 4 (28%) of 14 eyes had no visual field defect, 4 (28%) had early visual field defects, and 6 (43%) had severe visual field defects. Patients had a mean follow-up of 21.5 ± 9.0 years and experienced an average reduction of IOP by 28%. Four of 12 eyes (33%) had stable visual fields throughout follow-up, while 8 eyes (67%) had slow to moderate progression. The 30-2 and/or 24-2 HVF tests had an average change in MD of -0.53 ± 0.26 dB/year. No eyes had rapid progression with a MD > 1.0 dB/year. At final follow up, the mean IOP was 11.5 ± 2.9, and C/D ratio was 0.94 ± 0.4. At final follow up, 3 (21%) of 14 eyes had early visual field defects, 4 (29%) of 14 eyes had moderate visual field defects, and 7 (50%) had severe visual field defects. Six (43%) of 14 eyes met criteria for legal blindness.

Conclusions: We provide the first report of the clinical features and long-term clinical course in a family of NTG patients with TBK1 gene duplications. TBK1-associated glaucoma exhibits classic features of NTG. Patients present with severe disease at a relatively early age and most (67%) have slow to moderate progression of their visual field fields. The rate of visual field change appears correlated with the magnitude of IOP, suggesting that it may be advantageous to set extremely low IOP targets for some patients with TBK1-associated glaucoma.

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Department of Ophthalmology and Visual Sciences, University of Iowa

Session III – Paper 16

Clinical Spectrum of Autosomal Dominant Neovascular Inflammatory Vitreoretinopathy (ADNIV)

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Purpose: Autosomal dominant neovascular inflammatory vitreoretinopathy (ADNIV) is a rare, hereditary ocular condition caused by variants in *CAPN5*. The disease shares features of uveitis, pigmentary retinal degeneration, and proliferative retinopathy and demonstrates significant heterogeneity in clinical presentation. Here, we describe the clinical spectrum of disease in 4 distinct families with ADNIV.

Methods: This is an IRB-approved, retrospective chart review of patients seen at the University of Iowa with molecularly-confirmed ADNIV. Demographic data including age at presentation, gender, and genotype were recorded. Results from clinical examination including slit lamp and fundus examination were recorded, and data were extracted from clinical tests including best corrected visual acuity, Goldmann visual fields, optical coherence tomography, and electroretinography.

Results: A total of 130 eyes from 65 patients (69% female) were included in the study. The mean age at presentation was 41 years old (range, 6 to 77 years). The majority of patients (63.1%, 41/65) presented with excellent visual acuity (20/40 or better) in at least one eye. However, nine patients (13.8%) had bilateral, severe visual impairment on presentation (<20/200 in both eyes), and 5.4% (7/130) of eyes were phthisical or required enucleation. About half the of eyes (62/130, 47.7%) had vitreous cells, and 18.5% (24/130) had cystoid macular edema. Vitreomacular traction or epiretinal membranes were seen in 26.2% (34/130) of eyes, and a rhegmatogenous or tractional retinal detachment was seen in 9.7% (13/134) of eyes. Anterior segment neovascularization (10%; 13/130) and neovascular glaucoma (0.8%, 1/130) were relatively uncommon.

Conclusions: To our knowledge, this is the largest case series on ADNIV to date. The study demonstrates a wide clinical spectrum in ADNIV, with the majority of patients presenting with excellent visual acuity and half of eyes presented with vitreous inflammation. However, with increasing age, severe vision loss from complications including retinal detachment or phthisis are more common. The clinical heterogeneity suggests the presence of disease modifiers that merit further exploration.

Session III – Paper 17

Progression of Macular Atrophy and Phenotypic Variability in Autosomal Dominant Stargardt-like Macular Dystrophy Due to *PROM1* Genetic Mutation

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Primary supervisor: Elliott Sohn, MD
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Background: Autosomal dominant Stargardt-like macular dystrophy due to a mutation in prominin-1 (*PROM1*) is a rare, progressive, early onset retinal disease with high penetrance and variable phenotypic presentation. Numerous mutations have been reported, with the first and most prevalent being the p.R373C mutation which results in significant loss of central vision from macular atrophy starting in early adulthood. We aim to describe the natural history and phenotypic variability as well as establish rates of progression of geographic atrophy using multimodal imaging.

Methods: A single-center, longitudinal chart review of patients with a p.R373C mutation in the *PROM1* gene, established at the University of Iowa Hospitals and Clinics. Clinical records and multimodal imaging data were collected and analyzed. Age, best-corrected visual acuity (BCVA), funduscopic findings, visual field examination, fundus autofluorescence (FAF), and optical coherence tomography (OCT) data were used to characterize the disease. Manual delineation of atrophic areas on confocal scanning laser ophthalmoscope (SLO) images and OCT volume scans was performed by two independent graders and rates of atrophy progression were estimated for those with longitudinal imaging ≥12 months duration.

Results: Fifteen patients (3 male and 12 female) with an average age of 39 years (range 8 to 82) from six families were included in the study. Six patients (12 eyes) had at least two OCTs separated by at least 12 months enabling calculation of rates of ellipsoid zone and/or retinal pigment epithelium atrophy progression. The mean overall BCVA was 20/50 (range 20/15 - 20/1400) with an average presenting BCVA of 20/40 (range 20/15 – 20/320). Initial symptoms were reduced central acuity, first manifesting in the 2nd and 3rd decades of life. Yellow fundus flecks were seen in 13% of patients while mild, mid-peripheral nummular or bone-spicule-like pigmentation was seen in 73%. Phenotypic variability was observed with three distinct macular phenotypes noted: 1) central geographic atrophy (GA; 13%, n=2), 2) multifocal GA (20%, n=3), and 3) bull's eye maculopathy (BEM) (67% n=10); average rate of atrophy progression was 1.08 mm^2/year (SD=0.29); 0.53 mm^2/year (SD=0.31); 0.23 mm^2/year (SD=0.14), respectively. Overall average rate of atrophy progression was 0.36 mm^2/year (SD=0.32). OCT angiography demonstrated reduced retinal capillary density in the superficial and deep capillary plexi and choroidal flow loss corresponding with the areas of atrophy. OCT and FAF changes were seen as early as 8 years of age.

Conclusions: Patients with *PROM1*-associated macular dystrophy demonstrate phenotypic variability in the size and distribution of macular atrophy. The average rate of atrophy progression measured in our study is similar to reported rates for *ABCA4*-related Stargardt disease, and less than those typically reported for age-related macular degeneration. These findings are important for future novel therapeutics such as gene and stem-cell based retinal therapies and contribute to our understanding of mechanisms of geographic atrophy in various disease states.

Session III – Paper 18

Development of surgical technique and instrumentation for subretinal implantation of biodegradable photoreceptor cell delivery scaffolds

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Purpose: Photoreceptor and RPE cell losses are end stage features of heritable retinal diseases ranging from age-related macular degeneration (AMD) to retinitis pigmentosa (RP). To facilitate implantation of cellular scaffolds designed to transplant and sustain retinal progenitor cells, we evaluated surgical instruments and procedures that reliably deliver stem cell grafts in the porcine model.

Methods: Eyes of 2-6 month old pigs were assigned to one of 4 groups: non-vitrectomized controls (n=29), pars plana vitrectomy (PPV) surgical controls (n=15), or PPV with implantation of scaffolds (n=44). Implantation and surgical control eyes received PPV, balanced salt solution (BSS) bleb under the posterior retina, and diathermy creation of a linear retinotomy. Scaffold-implanted eyes additionally received poly(Ɛ-caprolactone) (PCL) or chitosan (CTS) biodegradable polymer placed in the subretinal space using one of two surgical instruments, injecting a 2x5x0.08 mm strip (n=19 eyes) or 5mm diameter 0.08 mm thick disc (n=25 eyes). All scaffolds implanted employed micro-wells capable of holding and protecting cells for transplantation. All surgical eyes received an air-fluid exchange (without long acting gases or laser to retinotomy). Ocular coherence tomography (OCT), histology and immunohistochemical imaging were performed at sacrifice (after 1-5 months). Data was analyzed using Mann-Whitney U test and Kruskal–Wallis one-way analysis of Variance for non-parametric data.

Results: Scaffolds were successfully inserted in each non-control eye. At sacrifice for eyes receiving scaffolds (controls shown in parenthesis), the findings included: retinal reattachment in 93% (93% without); severe uveitis in 0 (0 without); retinal fold in 7% (7% without); RPE atrophic changes 37% (64% without), and subretinal fibrosis in 44% (36% without); collateral retinal vessels were identified near the retinotomy in 17% of eyes with polymer (7% without); all p values were >0.05, i.e. non-significant. Preliminary histologic analysis revealed scaffolds within the subretinal space with preservation of overlying retina (n=9); eyes with polymer had mild to moderately increased GFAP staining around the polymer but were negative for immunologic markers IBA1, CD68 and IgG. Both the histology and immunohistochemical imaging showed attached retina with polymeric scaffold in place in the subretinal space and without inflammatory infiltrates.

Conclusions: Both delivery devices demonstrated a high rate of implantation success. Large posterior retinotomies closed spontaneously without laser, long-acting tamponade, or prone positioning. Both PCL and CTS scaffolds appear well tolerated in the subretinal space.