האגודה הישראלית לחקר העין והראיה
Israeli Society for Vision & Eye Research

PROGRAM
41st Annual Meeting

Online
10th-11th March, 2021

תכנית
הכנס השנתי ה-41
כנס מקוון

10-11 במרץ, 2021

עריכת התוכנית: דר׳ מיכל קרמר, דר׳ דידי פביאן, דר׳ יוסי מנדל
פרופ׳ איתי חוברס

עיצוב: דבורה מרקס אוחנה + עפרה חביב

ISRAELI SOCIETY FOR VISION AND EYE RESEARCH
The 41st Annual Meeting, March 10-11, 2021
Program at a glance

Wednesday, March 10 , 2021	
Session	**Time**
Opening remarks	**09:00 – 09:05**
Anterior Segment	**09:05 – 09:30**
Genetics	**09:30 – 10:00**
Visual function and neuro	**10:00 – 10:15**
Coffee Break	**10:15 - 10:25**
Panel- VOD lectures	**10:25 – 10:55**
Cataract	**10:55-11:15**
Retina	**11:10-11:40**
Evening plan	
Opening remarks	**19:00-19:05**
Guest lecture	**19:05-19:45**
Fichman Award Ceremony	**19:45-19:55**
Guest lecture	**19:55-20:30**
Closing remarks	**20:30-20:35**
Thursday, March 11 , 2021	
Glaucoma	**09:00 – 09:20**
Retina and Retinal degenerations	**09:20 – 09:50**
Oculoplastics and Oncology	**09:50 – 10:10**
Coffee Break	**10:10 – 10:20**
Business meeting and awards	**10:20 - 10:50**
Cornea	**10:50 – 11:10**
Pediatrics	**11:10 – 11:25**

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מרצים המקבלים השנה פרס על עבודות שהוצגו בכנס השנה שעברה (הכנס ה-40, 2020)

Award Recipients for the Best Papers Presented at the Previous Annual Meeting (the 40th Meeting, 2020)

מלגות נסיעה ל- ARVO ניתנות בעזרת מענקים שנתרמו באדיבות:
משפחת מרין לזכרו של פרופ' שאול מרין ז"ל
באדיבות פרופ' שני ועמותת "לראות".

Ruti Sela
Adhesion Strength and Rolling Properties of Descemet Membrane Endothelial Keratoplasty Grafts in a Rabbit Eye Model

Rivkah Lender
Cortical responses to prosthetic retinal stimulation are significantly affected by the light-adaptive state of the surrounding natural retina

Hadas Ketter-Katz
Migration of mononuclear phagocytes into the subretina contributes to retinal degeneration in the Leber congenital amaurosis RPE65/rd12 mouse model

Or Shmueli
Automatic detection of complete retinal pigment epithelium and outer retinal atrophy in optical coherence tomography scans using deep learning

Abstracts

תקצירים

1
Anterior segment
Live+VOD

Correcting a fundamental flaw in the paradigm for antimicrobial susceptibility testing

Lionel Sebbag (1;2), Victoria Broadbent (2), Danielle E. Kenne (2), Jonathan Mochel (2)
(1) Koret School of Veterinary Medicine, Hebrew University of Jerusalem, Rehovot, Israel (2) Iowa State University, College of Veterinary Medicine, Ames, Iowa, USA

Purpose. This study aimed to enhance the correlation between in vitro antimicrobial susceptibility testing (AST) and in vivo clinical environments. The ocular surface of diseased eyes contains high levels of serum albumin, a finding that is not accounted for when using the standard test medium for AST.

Methods. Minimum inhibitory concentration (MIC) susceptibility testing was performed for 17 different ophthalmic antibiotics (eg., chloramphenicol, ofloxacin, cefazolin), 30 bacterial isolates from canine patients (10 Staphylococcus pseudintermedius, 10 Streptococcus canis, 10 Pseudomonas aeruginosa), in the absence (0%) or presence of albumin (0.01 to 2%). Clinical interpretations (susceptible, intermediate, resistant) were determined with MIC breakpoints provided by the Clinical and Laboratory Standards Institute (CLSI).

Results. Variations in MICs and clinical interpretations were noted for 11/17 antibiotics following addition of albumin to the test medium. Albumin levels ≥ 0.1% increased MIC50 and MIC90 in dose-dependent, bacteria-specific and antibiotic-specific manner. Antibiotics most affected by albumin were erythromycin (8-fold increased MIC50) and tobramycin (4-fold increased MIC90) for Staphylococcus pseudintermedius, doxycycline (4.2-fold increased MIC50) for Streptococcus canis, and Ticarcillin (4-fold increased MIC50) for Pseudomonas aeruginosa.

Conclusions. Albumin impacts the efficacy of selected antibiotics as only the unbound portion of an antibiotic is microbiologically active. The present findings could improve decision making of clinicians managing bacterial keratitis, reduce development of antimicrobial resistance, influence current guidelines set by CLSI, and serve as a reference for bacteriological evaluations across medical fields and across species.

The prevalence of corneal abnormalities in first-degree relatives of patients with keratoconus: a prospective case-control study

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Purpose: Although there is a high prevalence of keratoconus in the Middle East including Israel, limited data is available describing first-degree relatives of patients with sporadic keratoconus (KC) using Scheimpflug imaging. The purpose of this study is to accurately phenotype first-degree relatives of patients with sporadic KC in Israel using corneal tomography, which may help determine the genetic etiology of KC.

Methods: First-degree relatives (N=56) of 16 KC probands participated in this prospective case-control study. Healthy controls (N=96) were from a previous study. Autorefraction, visual acuity, slit lamp biomicroscopy, retinoscopy, subjective refraction and Scheimpflug imaging (Sirius, CSO) of keratoconus patients and their first-degree relatives were evaluated. The worse eye was used for KC and KC suspects. The main outcome measure was prevalence of abnormal corneal topography and tomography parameters which was compared between first-degree relatives vs. controls. P values <0.05 were considered significant.¶

Results: KC (N=2) or KC suspect (N=8) was diagnosed in 18% (95% CI 8-28%) of the first-degree relatives. At least one abnormal corneal parameter was evident in 34% of first-degree relatives, while this was significantly lower for controls (14%,²‡ˇ(1, N=152) =8.8, P=0.01). Qualitative analysis showed KC first-degree relatives had significantly more abnormal anterior corneal topography patterns than controls (34% vs. 17%,²‡ˇ(1, N=152) =5.9, P=0.02). For first-degree relatives, sex was not a factor influencing prevalence of corneal abnormalities (18% for both men and women,1)²‡ˇ, N=56) =0.0, P=1.0). A significant correlation was found for first-degree relatives between age and most corneal parameters, while this was not evident for the control group.

Conclusions: Eye care practitioners should consider first-degree relatives of patients with KC at moderate risk for the disease and/or corneal abnormalities.

3
Cornea
Live+VOD

Metaherpetic disease in cats naturally exposed to feline herpesvirus type-1: Newly recognized pathology with translational potential to humans

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Purpose. Metaherpetic disease is recognized in humans affected by herpes simplex virus-1 but is not reported in cats affected by feline herpesvirus-1 (FHV-1) despite the high prevalence of herpetic disease in this species and strong similarities in viral biology between alphaherpesviruses of humans and cats. ¶

Methods. This preliminary work evaluated cats na¯ve to FHV-1 (n=9 cats, 18 eyes; control population) and cats naturally exposed to FHV-1 (n=4 cats, 7 eyes), as confirmed by serologic testing and review of medical records. Ante-mortem assessment included clinical scoring, blink rate, corneal aesthesiometry, tear film breakup time (TFBUT), and Schirmer tear test-1 (STT-1) with or without the nasolacrimal reflex. Post-mortem assessment involved confocal microscopy of the corneas and evaluation of corneal nerves with ImageJ. Groups were compared with Student's t tests and results are presented as mean±standard deviation.

Results. Compared to control, herpetic cats had significantly higher (P≤0.010) clinical scores (0.2±0.4 vs. 4.6±2.8) and response to nasolacrimal stimulation (7.8±10.8% vs. 104.8±151.1%), significantly lower (P<0.001) corneal sensitivity (2.9±0.6 cm vs. 1.4±0.9 cm), STT-1 (20.8±2.6 mm/min vs. 10.6±6.0 mm/min), TFBUT (12.1±2.0 sec vs. 7.1±2.9 sec), and non-significantly lower blink rate (3.0±1.5 blinks/min vs. 2.7±0.5 blinks/min; P=0.751). All parameters evaluated for corneal nerves (e.g., nerve fiber density, branching, occupancy) were notably but not significantly lower in herpetic vs. control cats (P≥0.268).

Conc lusions. In sum, cats exposed to FHV-1 had signs suggestive of corneal hypoesthesia and quantitative/qualitative tear film deficiencies when compared to cats na¯ve to the virus. It is possible these are signs of metaherpetic disease as reported in other species.

4
Anterior segment
Live+VOD

Long-term outcome of aflibercept subconjuctival treatment for chemical induced corneal neovascularization in the rabbit model

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Purpose: The dynamic course of sulfur mustard (SM) induced ocular insult is characterized by an acute phase, which may be continued to a chronic phase or a quiescent period followed by a late pathology. The aim of this study was to evaluate the efficacy of ziv-aflibercept (Zaltrap) or aflibercept (Eylea) in preventing or ameliorating the corneal insult in general and specifically the late phase induced neovascularization following ocular exposure to SM in the rabbit model.

Methods: Chemical SM burn was induced in the right eyes of NZW rabbits by vapor exposure. Zaltrap (2mg) was applied once by subconjunctival injection at 2h, 9 days or at 4 weeks post exposure. Eylea (2mg), the ocular specific preparation, was administered 4 weeks post SM exposure and following an initial one week treatment with 0.1% dexamethasone.

Non-treated exposed eyes served as controls. A clinical follow-up was performed for up-to 5-12 weeks following exposure and digital photographs of the cornea were taken for measurement of blood vessel length using an image analysis software. Eyes were taken for histological evaluation and extent of NV was determined by using H&E and Masson Trichrome staining.

Results: A single subconjunctival treatment of VEGF-trap 2h or 9 days post exposure presented a slight benefit in reducing the severity of the injury and in postponing the late induced NV growth. However in the group receiving treatment at 4 weeks following exposure, a significant reduced extent of existing NV was already seen at one week following injection, an effect which lasted for at least 8 weeks. The extensive reduction in existing corneal NV in the VEGF-trap treated group was confirmed by histological evaluation. Finally, eyes receiving the steroidal treatment during the first week and the ocular preparation of VEGF-trap following NV detection presented a significant reduction in corneal NV as compared to the steroid only treated group.

Conclusions: Subconjunctival Zaltrap or the combination of dexamethasone followed by Eylea treatment presented a long-term significant benefit in corneal NV reduction following ocular chemical exposure when used against existing NV rather than as a post exposure prophylactic treatment. These findings show the robust anti-angiogenic efficacy of both Eylea and Zaltrap and demonstrate the advantage of this treatment, in ameliorating corneal NV and protecting the ocular surface.

5
Visual function
VOD

Optimal rotation speed for maximum visual acuity using dynamic rotating optotypes

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Introduction: Everyday visual experience involves dynamic objects. However, standard visual acuity (VA) charts contain stationary optotypes that measure recognition acuity. The dynamic optotype (DYOP) VA chart (Chart 2020®) measures motion discrimination of a spinning optotype, and more closely resembles daily experiences. Additionally, DYOPs are devoid of recognition bias or memorization issues, and do not require literacy. Previous studies showed a relationship between rotation speed of Landolt Cs and VA. The goal of this study was to examine the relationship between DYOP rotation speed and VA.

Methods: The VA of healthy participants was measured in random order, two times for each of three rotation speeds (10, 40 and 100 revolutions per minute (RPM)) at 50% contrast, on a 60 Hz, 17"LCD monitor, at a distance of three meters. Participants requiring a refractive correction were randomly examined both in the corrected and uncorrected states. In a two-alternative forced choice paradigm, participants were asked to determine which optotype is spinning and its direction (clockwise or counter-clockwise). Optotype size was reduced after each correct response. The final VA was the target size in which only three of five presentations were correctly identified. VA outcomes of emmetropes and corrected ametropes (group 1) were analyzed separately from outcomes of uncorrected ametropes (group 2). For each sub-group, the VA obtained for each RPM was compared using repeated measures ANOVA.

Results: The study included 75 participants (51 female, 38 ametropes, mean age: 23.87±4.01, range: 18-38). The mean LogMAR VA was significantly better ($p < 0.02$) in the 40 RPM condition compared with the 10 and 100 RPM conditions for both sub-groups (10RPM: 0.13±0.11 and 0.5040 ,±0.24 RPM: 0.02±0.12 and 0.46100 ,±0.25 RPM: 0.08±0.15, and 0.59±0.28, for group 1 and group 2, respectively).

Conclusions: This study found a significant relationship between rotation speed of dynamic optotypes and VA. Similarly to previous studies, our study showed that 40 RPM provided the best VA. This rotation is the default rotation speed of DYOPs in Chart2020®.

Change in Eyelid Position between Photopic and Scotopic Conditions Suggests an Eyelid-Light Reflex

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Background: The physiologic function of the Müller's muscle have not been clearly defined. The purpose of the current study was to evaluate change in upper eyelid position between photopic and scotopic conditions.

Methods: A video scan of the anterior segment of 33 healthy subjects was performed using OCT infra-red mode in photopic and scotopic conditions and the transition between the two. The pupil diameter (PD), MRD1, MRD2 and vertical palpebral fissure height were measured.

Results: An increase in MRD1 was observed in 29 of 34 subjects (87.9%) following transition from photopic to scotopic conditions with a mean change of 348±311 microns ($P<0.0001$). The mean PD increased from 3,483±521 to 6,135±703 microns.

Conclusions: Eyelid retraction occurs after transition from photopic to scotopic conditions. This movement is synchronized with pupillary dilation, suggesting the existence of an "eyelid-light reflex" involving the Müller's muscle. The physiologic purpose of this phenomenon may serve to adjust the position of the eyelids as the pupil dilates under scotopic conditions.

7
Cornea
Live+VOD

Digital Eye Strain Symptoms During Online Learning Due to the COVID-19 Pandemic

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Purpose: Due to the COVID-19 pandemic, university students spend many hours in front of digital displays attending online classes. Digital displays differ significantly from printed materials and often result in symptoms known as â€œdigital eye strainâ€• (DES). This study examined the symptoms of DES in university students in Israel and New York during online learning.

Methods: The English and Hebrew translated DES and Ocular Surface Disease Index (OSDI) dry eye questionnaires were inserted into Google Forms. OSDI was included to determine if the symptoms were due to pre-existing dry eye disease. Questionnaires were sent to university students by email and social media. Non- university students, participants with self-reported ocular infections or prior ocular surgery, and those not attending online studies were excluded. Questionnaire results were analyzed using descriptive statistics, with scores above 5 considered symptomatic. Mann Whitney U-test was applied to compare the samples.

Results: Of the Israeli cohort, 160 of 164 participants met the inclusion criteria (38 were optometry students, 24 male, mean age: 26±8). The USA cohort consisted of 73 first year optometry students (15 male, mean age: 24.5±2.5). Respondents reported spending 18±9 hours and 17±7 hours per week in online studies, with 7±7 and 10±3 daily hours on their computer, and 6±9 and 5±3 daily hours on their cell phones in the Israeli and USA cohorts, respectively. The most frequently reported symptoms during or immediately after online studies in the Israeli and USA cohorts included eye fatigue (60% and 51%), eye strain (58% and 37%), ocular discomfort (44% and 34%), headaches (43% and 32%), dry eyes (39% and 34%), and burning eyes (40% and 25%). These symptoms were all significantly correlated with hours spent on the computer, though the prevalence of ocular eye strain, headaches, and dry eyes varied significantly between the cohorts ($p<0.05$). The prevalence of these symptoms far surpasses the typical prevalence of mild to severe dry eye (15% in the Israeli cohort, 10% in the USA cohort).

Conclusions: Results demonstrate a high prevalence of DES symptoms in university students. In the future, a causative relationship with digital displays can be established by comparing responses to symptoms reported during live learning. Healthcare providers should educate patients about ways to reduce DES.

Kelly Punch Punctoplasty and Simple Punctal Dilatation Are Equally Effective for Punctal Stenosis - A Randomized Prospective Study

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Purpose: To examine the clinical, imaging, and histopathological differences between Kelly punch punctoplasty and punctal dilatation, both with mini Monoka stent insertion.

Methods: This is a prospective, randomized, comparative clinical study. Patients with bilateral punctal stenosis and for whom surgery was advised participated in the study. The right eye underwent Kelly punch punctoplasty and the left eye simple punctal dilatation, both with mini Monoka stents were participated. Data were collected and analyzed before and 3 months following the procedure and included the degree of epiphora (Munk score) and punctal size as measured by anterior segment optical coherence tomography (AC-OCT). All specimens removed by the Kelly punch punctoplasty were sent for histopathologic evaluation, including Masson's trichome muscle staining.

Results: The study included 46 eyes of 23 patients (4 males, 19 females) whose mean age at presentation was 60.43±14.81 years (range 19-84 years). There was a significant decrease in the Munk score after both punctoplasties compared to baseline values ($P < 0.01$, matched pairs). There was no significant differences between groups in delta Munk score. There was a significant increase in punctal size after both procedures compared to baseline values as measured by AS-OCT. The Riolan muscle was visible in only 3 of the 23 (13.04%) specimens from patients who underwent the Kelly punch punctoplasty.

Conclusions: The Kelly punch punctoplasty and the simple dilator punctoplasty, both with stents, are equally effective treatments for epiphora due to acquired punctal stenosis. Only few specimens removed during the Kelly punch method show muscle fibers.

Quality of life of patients with thyroid eye disease: three-year follow-up in a multidisciplinary clinic

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Sheba Medical Center, Tel-Hashomer, affiliated to the Sackler Faculty of Medicine, Tel-Aviv University, Tel Aviv

Background: Changes in the quality of life (QOL) of patients with thyroid eye disease (TED) were examined during a 3-year follow-up in a multidisciplinary eye clinic, and factors that may improve QOL were identified.

Method A retrospective review of medical records of all patients who attended the TED clinic at Sheba Medical Center from May 2016 to May 2019 was performed. The retrieved data included demographics, comprehensive ophthalmic examination findings, clinical activity scores (CAS), laboratory test results, and QOL assessments by the Gravesג€™ Orbitopathy QOL questionnaire (GO-QOL).

Results One-hundred and thirty-two TED clinic patients were examined. Thirty patients (22.72%) received medical treatment consisting of steroids according to the European Group on Gravesג€™ Orbitopathy (EUGOGO) protocol, high-dose steroids, or immunosuppressive drugs. Twenty-eight patients (21.21%) underwent surgical rehabilitation (decompression, strabismus, or eyelid surgery). There was a significant increase in total QOL score after steroid treatment according to the EUGOGO protocol, after decompression surgery, and after strabismus surgery compared to pre-treatment total QOL (p=0.04, p=0.021, and p=0.042, respectively, matched pairs). In addition, there were significant positive correlations between the changes in the total QOL score and the change in thyroid-stimulating immunoglobulin (TSI) as well as the change in CAS among the patients who underwent medical and surgical interventions.

Conclusions QOL should be taken into account when considering medical or surgical interventions in TED patients. A change in the CAS and in the TSI may also correlate with change in QOL. Periodic evaluation of TED patientsג€™ QOL is recommended for enhanced and more comprehensive management.

10
Retina
VOD

Optical coherence tomography prognostic factors in AMD patients with peripapillary macular neovascularization â€“ one year follow-up

Anfisa Ayalon [1], Gilad Rabina [2] , Michael Mimouni [3], Nir Stanescu [4], Elad Moisseiev [1], Arie Y Nemet [1], Noa Geffen [5] , Ori Segal [1].
[1] Ophthalmology department, Meir Medical Center, Kfar Saba. [2] Ophthalmology department, Tel Aviv Sourasky Medical Center, Tel Aviv. [3] Ophthalmology department, Rambam Medical Center, Haifa. [4] Ophthalmology department, Assuta Medical Center, Ashdod. [5] Ophthalmology department, Rabin Medical Center, Petah Tikva.

Purpose: To investigate the correlation between optical coherence tomography (OCT) findings and visual acuity outcomes after treatment with intravitreal bevacizumab (IVB) injections for age related macular degeneration (AMD) patients with peripapillary macular neovascularization (PPMNV).

METHODS: A retrospective case series of consecutive patients diagnosed with PPMNV secondary to AMD. All patients treated with IVB injections with a follow-up time of one year. Data collected included best corrected visual acuity (BCVA), average central retinal thickness (CRT), maximum CRT (max CRT), minimum CRT (min CRT), choroidal thickness, maximum height and area of sub retinal fluid (SRF), intra retinal fluid (IRF), pigment epithelium detachment (PED) and subretinal hyperreflective material (SHRM).

RESULTS: A total of 68 eyes were diagnosed with PPMV during the study period, of them, 30 eyes of 30 patients aged 84.3±6.9 years of which 63.3% female gender were included. Baseline BCVA was 0.46±0.62 logMAR, average choroidal thcikness was 193.2±22µm and mean number of IVB injections was 7.2±1.9. After one year BCVA was 0.56±0.78 logMAR (p=0.28). Eyes with greater CRT (r=-0.36, p=0.05), min CRT (r=-0.45, p=0.01), max CRT (r=-0.39, p=0.04), SHRM area (r=-0.37, p=0.05) and SRF area (r=-0.73, p<0.001) had a significantly smaller improvement in BCVA at one year. Eyes with PED (0.68±0.90 versus 0.21±0.12, p=0.03) had a significantly worse final BCVA.

CONCLUSIONS: Our data suggests that PPMNV, AMD related, with greater foveal thickness, PED size, SHRM and SRF areas have worse final BCVA prognosis.

11
Cornea
Live+VOD

Evaluation of Incomplete Blinking as a Measurement of Dry Eye Disease

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Background: The association between partial blinking during spontaneous blinking as measured by interferometry and ocular exams for the assessment of mild-to-moderate dry eye disease (DED) has not been well established.

Methods: This retrospective study included 58 eyes of patients previously diagnosed with DED. Ocular surface assessment included ocular surface disease index (OSDI) score, tear film osmolarity, tear breakup time (TBUT), grading of corneal fluorescein staining, the Schirmer I test, and dry eye parameters by the LipiViewλ„¢ interferometer (TearScience, Morrisville, NC, USA), including average lipid layer thickness of the tear film (LLT), meibomian gland dropout (MGd), number of incomplete and complete blinks per 20 seconds and the partial blinking rate (PBR). Generalized estimation equations (GEE) were used for association testing between each variable of interest. The working correlation for each GEE model was selected using the Corrected Quasi-likelihood under the Independence Model Criterion.

Results: The number of incomplete blinks was significantly associated with TBUT (P=0.006), OSDI (P=0.000) and MGd (P=0.000). PBR was significantly associated with OSDI (P=0.032) and MGd (P=0.000). The number of complete blinks was significantly associated with TBUT (P=0.032), but not with other ocular surface parameters. MGd was significantly associated with TBUT (P=0.002) and OSDI (P=0.001). LLT was significantly associated with tear film osmolarity (P=0.007), and tear film osmolarity was significantly associated with LLT (P=0.000).

Conclusions: Incomplete blinking is associated with decreased TBUT, increased OSDI, and increased MGd possibly through its contribution to meibomian gland obstruction and subsequent loss of tear film homeostasis. It may therefore be considered an additive measure for mild-to-moderate DED assessment.

12
Retina
Live+VOD

Safety Margins of Anti-VEGF Therapy using Treat and Extend Treatment Protocol - Lessons from the COVID-19 Pandemic

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Hadassah Medical center, Ophthalmology Department, Jerusalem

PURPOSE:To analyze the consequences of delaying intravitreal (IVI) anti-vascular endothelial growth factor (VEGF) therapy in patients under treat-and-extend (TAE) protocol.

METHODS: Retrospective review of medical records of consecutive group of patients receiving IVI using TAE protocol before and during the COVID-19 pandemic. Data collected included diagnosis, demographics, treatment schedule, compound used, and anatomical outcome according to spectral domain optical coherence tomography (SD-OCT).

RESULTS: A total of 923 eyes (691 patients) were included; 58.8% (543 eyes) were treated for neovascular age-related macular degeneration (nvAMD), 25% (231 eyes) had diabetic macular edema (DME), and 16.2% (149 eyes) with retinal vein occlusion (RVO). Average patient age (±SD) was 74.511.7 ± years. Female/male ratio was 1.08:1. Delayed therapy during the pandemic (?7 days) occurred in 56.3% of the eyes. This included 56.2%, 61.5%, 49.0% of nvAMD, DME and RVO patients respectively. The overall average delay (±SD) was 15.3±23.4 days. RVO patients were on average less late (9.3±16.1 days) compared to nvAMD (15.8±23.8) and DME (18.2±25.6) eyes (P=0.002). Multivariate analysis showed that in nvAMD duration of the disease and type of anti-VEGF were predictors of number of days late (P=0.011 and 0.019). In eyes ? 7days late, 45.7%, 58.5% and 58.9% of nvAMD, DME and RVO eyes respectively showed increase in central subfield thickness (CST). Worsening was related to absolute numbers of days late, and not to the percentage of delay of the recommended interval. A positive correlation was found between delay to treatment and increase in CST.

CONCLUSIONS: Delaying IVI in eyes under TAE regimen was common during the COVID-19 pandemic. These delays were associated with macular thickening having potential visual consequences.

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VOD

Surgical Treatment of Ozurdex Implant Migrating to the Anterior Chamber

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Background: Ozurdex implant migration to the anterior chamber is a rare but serious complication, which without prompt treatment may result in permanent corneal endothelial injury. Risk factors include compromised zonules, posterior capsule defect, aphakia, anterior chamber IOL and iris defects.

Methods: We present a case of a 79 yo woman with persistent CME of combined etiology: Pseudophakic CME, secondary to a complicated cataract surgery with ACIOL and BRVO. This patient has been previously treated with multiple intravitreal injections of anti-VEGF agents with poor clinical and OCT response. After the successful, but transient response to an intravitreal injection of Triesence, a decision has been made to inject Ozurdex.

During the follow up visit, six weeks after the uneventful injection, the patient complained of decreased vision, however the OCT scan demonstrated a resolution of the CME. On examination, she had a red eye, decreased vision, an injected conjunctiva, and corneal edema. The Ozurdex implant was observed resting in the inferior aspect of the A/C.

Results: The patient was taken to the OR for removal of the migrated implant. There is a supplemental movie describing our surgical approach for this uncommon complication, using a regular 20G needle on a 2 CC syringe in a minimally invasive technique.

Conclusions: Following the removal of the implant, the corneal edema has completely resolved.
This presentation will also revise the indications and contraindications for the Ozurdex implant and suggested strategies for the removal of the implant from the A/C.

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Ten year functional and anatomical treatment outcome of neovascular age-related macular degeneration and association with the major risk alleles

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Purpose: To evaluate the long-term functional and anatomical outcomes of neovascular age-related macular degeneration (nvAMD) eyes treated with intravitreal anti-vascular endothelial growth factors (VEGF) compounds for up to 10 years and to identify associated factors.

Methods: Retrospective evaluation of consecutive nvAMD naïve eyes initially treated with intravitreal bevacizumab, and switched to ranibizumab or aflibercept if required using a treat and extend protocol. Data was collected from the electronic medical records including demographics, clinical, and optical coherence tomography findings. Genotyping for the CFH (rs1061170), HTRA1 (rs1200638), and C3 (rs2230199) major risk single nucleotide polymorphisms for AMD was collected.

Results: A total of 206 patients (n=276 eyes) commenced anti-VEGF therapy ‰¥8λ years, and 66 (32.0%) patients (n=80 eyes, 29.0%) remained in follow-up ‰¥8λ years and were included in this study. The mean number of anti-VEGF injections (±SD) was 73.3±28.0 over 10 years. Mean best-corrected visual acuity (BCVA) (LogMAR±SD) improved from 0.55±0.53 at baseline to 0.42 ±0.41(p<0.0005) at 24 months, but deteriorated to 0.81±0.71 at 8 years (p<0.03) and 1.00±0.73 at 10 years (p<0.0005, compared with baseline). Baseline central point thickness (CPT) and central subfield thickness (CST; microns±SD) were 410.9±208.1 and 415.8±162.1, respectively. Both values decreased to 294.7±135.9 and 323±113.6 (p<0.0005 in each case), respectively, after 3 monthly injections, and remained lower than baseline values until the end of follow-up. BCVA and intraretinal fluid at baseline, macular atrophy and thinning at end of follow-up were associated with the visual outcome after 10 years. Carriers of the CFH and C3 risk alleles had smaller reduction of CST at follow-up compared with none-carriers. Thinning of CST correlated negatively with the number of CFH/C3 risk alleles borne by a patient. (Pearson rho= -0.246, and -0.608; p=0.040, and 0.003 at 8 and 10 years, respectively).

Conclusion: nvAMD patient under anti-VEGF therapy for over 10 years encounter a substantial mean vision loss that is influenced by the presence of IRF at baseline and by atrophy rather than re-thickening of the macula at follow-up. Major complement risk alleles for AMD are associated with a lesser reduction in baseline macula thickness in the long-term.

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VOD

Could retinal tear laser retinopexy cause persistent macular edema?

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Background: New or exacerbated macular edema is a known complication of extensive laser treatment such as panretinal photocoagulation. The postulation is that laser treatment 3 with relapsing and remitting episodes of CME. Additional treatments included systemic corticosteroids and adjunct Ozurdex (dexamethasone 0.7 mg) implants, with favorable clinical response.

Due to the diagnosis of choroiditis, treatment paradigm was changed towards chronic immunosuppression.
Conclusion: To the best of our knowledge, no similar cases were previously published. We postulate that the laser treatment may have exacerbated a subclinical inflammatory condition, which could only be diagnosed at this situation by multimodal imaging.

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Pediatrics
Live+VOD

The dynamic optotype (DYOP): a new visual acuity test for use in children.

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Purpose To evaluate the Dynamic Optotype (DYOP), a simple visual acuity test based on a dynamic target that requires minimal knowledge of symbols and letters. The visual acuity results obtained from children using the Dynamic Optotype (DYOP) visual acuity were compared with results obtained using the Early Treatment Diabetic Retinopathy Study (ETDRS) Lea numbers chart.

Methods One-hundred-sixty children ages 4 to 17 years were recruited consecutively from the Pediatric Ophthalmology Unit of Meir Medical Center. Monocular visual acuity was tested using the new eye chart and the ETDRS chart, alternating the order of administration between children. Testing was performed on the eyes with the poorest acuity. Outcome measures were monocular logarithm of the minimum angle of resolution (logMAR) visual acuity scores for each chart.

Results The acuities had a strong linear correlation (r =0.88) with a mean difference in acuity of -0.01 (95% confidence interval (CI), -0.02 to 0.01) logMAR, equivalent of approximately less than one letter, with the DYOP test underestimating vision as determined by the ETDRS chart. The 95% limits of agreement were±1.2 lines.

Conclusions This study supports the validity of the new DYOP eye chart as a measure of visual acuity among pediatric patients ages 4 to 17 years, with vision ranging from 20/16 to 20/200.

Results of EDOF IOL implantation in the second eye of patients implanted previously with a monofocal IOL in the first eye

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Purpose: To investigate the visual results and patient's satisfaction after unilateral implantation of the Symfony intraocular lens (IOL) in the second eye of patients implanted previously with a monofocal IOL in the first eye, and to compare the results to patients implanted bilaterally with either the Symfony IOL or monofocal IOL.

Methods: Medical records and patientsλ€™ self-reported questionnaire of consecutive patients who were implanted with the Symfony IOL in the second eye and a monofocal IOL in the first eye (group A), bilateral Symfony IOL (group B) and bilateral monofocal IOL targeted for distance (group C) were compared retrospectively for visual outcome, spectacle independence, patient satisfac¬tion, and subjective photic phenomena.

Results: The patients in group A (18 eyes of 18 patients) had better distance uncorrected visual acuity compared with group B (72 eyes of 36 patients) and group C (44 eyes of 22 patients) ($p = 0.043$, $p = 0.002$, respectively), similar intermediate uncorrected visual acuity as group B, and a tendency towards better near uncorrected visual acuity compared with group C ($p=0.052$). No difference in complaints of haloes and/or glare was found between the groups.

Conclusion: Patients, previously implanted with a monofocal IOL in one eye that are interested in improving their spectacle independence can be considered for Symfony IOL implantation in the second eye with similar results to those implanted bilaterally with Symfony IOLs and better results than patients implanted bilaterally with monofocal IOLs.

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VOD

The 100 Most Frequently Cited Articles on Myopia

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Purpose: To identify the 100 most-cited publications on myopia and provide a historical perspective of this growing global epidemic.

Design: A bibliographic study.

Methods: The Web of Science Database was searched from 1999 to 2018. The recorded parameters included the journal name, impact factor, year and language of publication, number of authors, article origin and type, methodology, number of subjects, funding, and topics of the study.

Results: The articles were published in 27 ophthalmology journals. Investigative Ophthalmology Vision Sciences (28%) and Ophthalmology (26%) published the highest number. Asia produced the most publications (33%); the leading countries were the United States (20%), Australia (17%), and Singapore (11%). However, articles with a significantly higher mean rank came from the US and Singapore. The US had the highest mean number of citations, significantly more than Europe. The methodology of half of the papers was prospective. Epidemiological assessments were the leading type (28%). Etiology, signs and symptoms and treatment equally encompassed 80% of the topics. Papers on etiology equally addressed the genetic and environmental factors. Prevention dealt predominantly with public awareness (42%). Treatment included optical (39%), pharmacological (25%), and behavioral modifications (4%) to prevent myopia progression as well as refractive surgery (32%).

Conclusions: The US had the most publications; it had the highest mean rank and the highest mean number of citations. Prospective and epidemiological assessments were more common than others. Prevention was the least common topic. Optical treatment was the most popular modality and myopia control was more frequently addressed than refractive surgery.

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The Effect of Blue-Light Filtering Intraocular Lenses on the Development and Progression of Neovascular Age-Related Macular Degeneration

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Purpose: To assess the effect of blue-light filtering (BLF) intraocular lenses (IOLs) on the prevention of neovascular age-related macular degeneration (nAMD) after cataract surgery.

Methods: Patients who underwent uneventful cataract surgery between 2007 and 2018 were included. Subsequent nAMD rates were compared between patients who received BLF IOLs and those who received non-BLF IOLs. Kaplan-Meier and Cox regression analyses for the overall risk of nAMD developing were assessed. Best-corrected visual acuity (BCVA), foveal thickness, treatment interval, and total number of intravitreal injections were secondary outcomes. A separate analysis was performed on patients with pre-existing nAMD to assess the effect of BLF IOLs on nAMD progression. A single eye of each patient was included.

Results: Included were 11397 eyes of 11397 patients with a mean age of 75.4 8.3 ±¸ years (62.5% women). The BLF IOL was used in 5425 eyes (47.6%), and the non-BLF IOL was used in 5972 eyes (52.4%). During follow-up (BLF IOL group, 55.234.1 ±¸ months; non-BLF IOL group, 50.530.1 ±¸ months; P < 0.001), 164 cases of new-onset nAMD were recorded (BLF group, n = 88; non-BLF group, n = 76). The nAMD-free survival was similar between the groups (P = 0.465, log-rank test). In a Cox regression analysis controlling for age, gender, and a documented diagnosis of macular degeneration, the use of a BLF IOL was not predictive of nAMD development (hazard ratio [HR], 1.075; 95% confidence interval [CI], 0.79-1.47; P = 0.652). In nAMD patients, secondary clinical outcomes at 1 year were comparable for BCVA (0.570.4 ±¸ logarithm of the minimum angle of resolution vs. 0.45 ±¸ 0.4 logarithm of the minimum angle of resolution; P = 0.136), foveal thickness (285- 109 ±¸¼m vs. 299¸± 103-¼m; P = 0.527), number of anti-vascular endothelial growth factor injections (6.52.5 ±¸ vs. 6.22.7 ±¸; P = 0.548), and treatment interval (7.52.4 ±¸ weeks vs. 8.12.4 ±¸ weeks; P = 0.271) for BLF and non-BLF IOLs, respectively. Similarly to patients in whom nAMD developed after the surgery, among patients with nAMD before surgery (BLF, n = 71; non-BLF, n = 74), the clinical outcomes again were comparable (all P > 0.05).

Conclusions: In a large cohort of patients who underwent cataract surgery, the use of a BLF IOL resulted in no apparent advantage over a non-BLF IOL in the incidence of nAMD or its progression, nor in clinical variables related to nAMD severity.

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Visual results and patient satisfaction ofpresbyopia correcting IOLs - -first eye versus second eye

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Purpose: To investigate the visual results and patient satisfaction after the first eye surgery compared with the second eye surgery when presbyopia correcting IOLג€™s were implanted

Methods: A retrospective chart review of patients who underwent uneventful bilateral cataract surgery with PC IOL in the "Ein Tal" surgical center between 2015-2019, by two surgeons. One-month after the surgery a satisfaction questionnaire was filled in. Data analysis was divided to 2 groups according to the IOL implanted: Multifocal IOL (MIOL) and Extended depth of focus (EDOF).

Results: One hundred and ninety-seven eyes underwent PC IOL implantation (103 EDOF, 94 MIOL). There was no difference in the objective refractive and visual results after the first and second surgery.

For the MIOL group there was statistically significant improvement the number of patients reporting good or excellent visual acuity for all ranges ($P<0.05$). spectacle independence for intermediate, near and overall significantly improved ($P<0.01$).
For the EDOF IOL group only the near visual acuity improved significantly after the second eye operation ($P<0.05$). spectacle independence improved for all ranges ($P<0.05$). In both groups photopic phenomena and overall satisfaction had no significant difference.

Conclusion: Patients In both groups reported better visual acuity and less spectacle dependence after the second eye operation. Unsatisfied patients after implantation of presbyopia correcting IOL's in their first eye operation can be encouraged that an operation on the second eye has a good chance to improve their subjective perception of their visual acuity and reduce their need for spectacles.

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Live+VOD

Ocular Manifestations of Ectodermal Dysplasia

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Purpose: The ectodermal dysplasias (EDs) constitute a group of disorders characterized by abnormalities in two or more ectodermal derivatives, including skin, hair, teeth, and sweat glands. The purpose of the current study was to evaluate ocular manifestations in pediatric patients with ED.

Methods: Retrospective case series including consecutive ED subjects who were treated in the ophthalmology department at the Children’s Hospital of Philadelphia over a 12-year period (2009-2020). Main Outcome Measures were ocular and ocular adnexal abnormalities.

Results: Thirty subjects were included: 20 males (67%), mean age of 4.5 years (range,0.3-18). Diagnoses were as follows: hypohidrotic ED in 8 patients (HED) (27% of all patients), hidrotic ED (n=2/30, 7%), ectrodactyly-ectodermal dysplasia-clefting (EEC) (n=8/30, 27%), ankyloblepharon-ectodermal defects-cleft lip/palate (AEC) (n=3/30, 10%), Rapp-Hodgkin ED (n=2/30, 7%), Marshall syndrome (n=2/30, 7%), unspecified ED (n=2/30, 7%), ED with immunodeficiency (n=1/30, 3%), tricho-dento-osseous syndrome (n=1/30, 3%), and oculo-ectodermal syndrome (OES)

(n=1/30, 3%). The most common presenting symptoms were tearing, occurring in 14 subjects (47%), followed by photophobia in 6 (20%). Most common findings were: lacrimal drainage obstruction in 12 (40%) including punctal agenesis in 10 (33%), refractive errors in 13 (43%) and amblyopia in 6 (20%).
A new occurrence of eyelid ptosis or eyelash ptosis was demonstrated in 11 subjects (37%), all had TP63 or EDA1 genes mutations.
Twelve subjects (40%) underwent surgical intervention, most commonly lacrimal surgery which was performed in 7 patients (23%), and eyelid surgery in 5 patients (20%).

Conclusions: Ectodermal dysplasias are associated with various ocular and ocular adnexal abnormalities. In this series, several new findings were observed, including increased risk of amblyopia in most subtypes, as well as eyelid ptosis and lash ptosis in subtypes with TP63 or EDA1 gene mutations. In addition, trichiasis may be more common in AEC than previously described, and posterior pole osteomas and peripapillary colobomas may be found with OES. These various findings mandate early ophthalmic evaluation in this unique group of children.

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Pediatric Acute Dacryocystitis

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Purpose: To analyze the clinical presentation, course, and management in a large cohort of pediatric acute dacryocystitis (PAD) subjects, and to examine whether hospitalization and urgent surgical intervention are indeed mandatory.

Methods: A retrospective analyzis of all pediatric subjects diagnosed with dacryocystitis at the Children›€™s Hospital of Philadelphia over a 12-year period (2009-2020).

Results: 169 PAD patients were included in this study. Management included admission in 117 cases (69%). Sixty-eight patients (40%) were treated medically with no surgical intervention, 75 cases (44%) required urgent surgical intervention, and 26 additional cases (15%) required surgery due to persistent tearing symptoms after medical management. The urgent procedures included most commonly:(1) Endonasal examination and microdebridement of intranasal cysts (EM) in 26 cases (35%); (2) probing and irrigation without EM, with or without stent intubation, in 30 cases (40%) and (3) Dacryocystorhinostomy (13 endonasal and 4 external) in 17 cases (23%).

Conclusions: Management of pediatric acute dacryocystitis should be tailored individually for each case. Hospital admission and early surgical intervention are not mandatory, as 31% of cases resolved without admission, and 56% without early surgical intervention. Although a specific age cutoff is not plausible, hospital admission for younger patients is more commonly advocated. When surgical intervention is indicated, endonasal examination and microdebridement of any associated intranasal cyst as well as probing with possible stenting are the initial procedures of choice. Dacryocystorhinostomy is reserved for more complex obstructions. Although PAD is an infection with serious potential problems, when managed appropriately, complications are rare.

Blepharophimosis-Plus Syndromes: Incidence of Systemic Genetic Disorders in Blepharophimosis

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Purpose: Blepharophimosis is a cardinal feature of blepharophimosis-ptosis-epicanthus inversus syndrome (BPES), a condition caused by heterozygous variants in the FOXL2 gene. Although blepharophimosis most frequently indicates underlying BPES, there are other syndromes associated with blepharophimosis that should be considered as part of the clinical spectrum. The purpose of this study was to determine the incidence of systemic genetic disorders in patients presenting with blepharophimosis .

Methods: A retrospective medical records review of all consecutive cases of blepharophimosis seen in the ophthalmology division at the Children's Hospital of Philadelphia in a 12-year-period (2009-2020) was performed. Main outcome measures were genetic diagnosis in children with blepharophimosis.

Results: 135 patients with blepharophimosis were included, 72 females (n=72/135, 53%) and 63 males (n=63/135, 47%). Average age on first visit 3.5 years (SD 6.4, range 0-39.8 years). Sixty-seven of patients (n=67/135, 50%) had genetic testing for FOXL2 gene mutation; 54 cases (n=54/67, 81%) had FOXL2-related gene mutation, while 13 cases (n=13/67, 19%) did not. Altogether, 126 patients (n=126/135, 93%) had a final diagnosis of solely BPES, while nine subjects (n=9/135, 7%) were diagnosed with systemic or other syndromic disorders. Of these 9 cases, six were diagnosed with a classic Mendelian syndrome, including: Dubowitz syndrome (n=2), Ohdo syndrome (n=1), 22q11.2 duplication (n=1), and 3q22 deletion (n=2); three patients had multiple systemic abnormalities but a definite genetic diagnosis was not achieved.

Conclusions: Blepharophimosis is an eyelid feature of several genetic disorders, including but not exclusive to isolated BPES. A comprehensive genetic evaluation is therefore justified in all cases, especially those with multi-organ involvement. As the ophthalmologist is often the first provider to recognize these unique features, consideration of other syndromes is critical to providing complete patient care.

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Ocular Manifestations in Pediatric Patients with Koolen-de-Vries Syndrome

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Purpose: Koolen-de Vries syndrome (KdVS) (OMIM #610443) or 17q21.31 microdeletion syndrome, is a rare genetic disorder characterized by developmental and speech delay, intellectual disability, epilepsy, hypotonia, characteristic facial features, and congenital malformations of multiple organs.

The purpose of the current study was to describe ocular manifestations and surgical interventions in six KdVS pediatric patients, and to review the ocular associations of this condition.

Methods: A retrospective review of consecutive KdVS subjects who were treated in the ophthalmology department at The Children’s Hospital of Philadelphia over a 12-year period (2009-2020) was performed. Main Outcome Measures were ocular and ocular adnexal abnormalities, and ophthalmic surgical interventions.

Results: Six patients were included (4 females (67%), mean age of 3.1 years (range 0.1 to 8.1 years)). The most common ocular findings were strabismus (n=3/6, 50%), ptosis (n=3/6, 50%), and hyperopia (n=3/6, 50%). Two patients had amblyopia. Four patients required surgical intervention, including strabismus repair (n=3), and bilateral levator resection and medial canthopexies (n=1).

Conclusions: KdVS is associated with various ocular and ocular adnexal abnormalities. Most commonly ptosis, strabismus and hyperopia. Most cases required surgical intervention, most commonly strabismus repair. These findings mandate early ophthalmic evaluation with regular follow-up in this unique group of children.

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Visual function
Live+VOD

Naturally-occurring myopia and loss of cone function in a sheep model of achromatopsia

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Purpose: Achromatopsia is an inherited retinal disorder characterized by loss of cone photoreceptor function. Day blind CNGA3 mutant Improved-Awassi sheep provide a naturally occurring large animal model for the disease and have previously been utilized by our group for gene augmentation therapy trials. The purpose of the current study was to measure refractive error and axial length parameters of this model, and evaluate chromatic pupillary light reflex (cPLR) testing as a potential screening test for loss of cone function.

Methods: Three cohorts of sheep were examined and compared. 21 CNGA3 mutant, Improved-Awassi sheep, 12 control wild type Afec-Assaf sheep raised under the same intensive husbandry management and 12 control wild type breed-matched Local-Awassi sheep raised under extensive husbandry conditions. Sheep were examined using streak retinoscopy, axial length parameters were measured using B-mode ocular ultrasonography, and cPLR was used to evaluate pupillary reflexes.

Results: Day blind, CNGA3 mutant sheep were found to be significantly more myopic (H meridian: -2.150.31 ±♀ D , V meridian: -1.520.29 ±♀ D) than both control groups (H meridians: -1.120.42 ±♀ D and 1.060.42 ±♀ D; V meridians: -0.270.38 ±♀ D and 0.62♀± 0.38 D), and had significantly longer vitreous axial length compared to breed matched control group (1.430.13 ±♀ vs. 1.23 ±♀ 0.06 cm). Day blind sheep Lack pupillary response to bright red illumination compared to control sheep, but exhibit normal responses to bright blue and white illumination, consistent with cone dysfunction and intact inner retina.

Conclusions: Day blind sheep were found to exhibit myopia and increased vitreous chamber depth, providing a naturally occurring large animal model of myopia, the leading cause of vision impairment worldwide. cPLR can be used as a screening test to diagnose day blindness in sheep.

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Glaucoma
Live+VOD

Automated Direct Selective Laser Trabeculoplasty: First Prospective Clinical Trial

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Purpose: Direct selective laser trabeculoplasty (DSLT) is a rapid, non-contact automated procedure performed directly through the limbus without gonioscopy. In this first non-randomized clinical trial to assess its safety and ability to reduce intraocular pressure (IOP).

Methods: Fifteen patients (15 eyes: 10 with open-angle glaucoma (OAG), 4 with ocular hypertension, and one with pseudoexfoliation glaucoma) , naïve or after medication washout, with an IOP ≥22 mmHg, underwent DSLT by irradiation with 100 or 120 sequential non-contact 532 nm, Q-switched laser shots (0.8−1.4 mJ) automatically applied during 1.5 or 2.3 seconds on the limbus, guided by image analysis and eye tracking. Results were assessed at 1 and 3 hours, 1 day, 1 week, and 1, 3, and 6 months.

Results: The mean ± standard deviation baseline IOP (mmHg) in all eyes was 26.7±2.3. At 1, 3, and 6 months, this value was significantly reduced to 21.7±4.2 (by 18.1%), to 20.8±2.5 (by 21.4%), and to 21.5±4.1 (by 18.8%), respectively. In 6 patients treated with 1.4 mJ/shot, the mean IOP at 6 months decreased from 26.7±3.2 to 19.3±2.0 (27.1%, P=0.03). There was a significant reduction in hypotensive medications (from 1.6±1.0 to 0.4±0.7, P=0.03). No serious adverse events occurred. **Conclusions**: Automated DSLT appears to be an effective and safe non-contact, rapid modality for reducing IOP in patients with OAG. Higher energy usage led to better results.

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Visual function
Live+VOD

Short Term Visual Related Ocular Effects During Treatment with D-MPH for ADHD

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Objective: To evaluate the short-term effect of dexmethylphenidate (D-MPH) on visual acuity, pupil size, anterior chamber depth (ACD), and accommodation-convergence reflex in children treated with D-MPH for attention-deficit/hyperactivity disorder (ADHD).

Method: Prospective cohort study including 15 patients aged 8-16 (11.58±2.39) treated with D-MPH for ADHD. Patients were questioned for subjective complains such as blurred vision and photosensitivity. Ophthalmic evaluation was performed prior to and 1.5 hours following D-MPH administration. The exam included evaluation of visual acuity at distance and near, accommodation range, convergence range, 3-D vision test and anterior chamber optical coherence tomography (OCT).

Results: A significant association between pupil diameter and D-MPH dosage was demonstrated (p=0.001). Additionally, a positive correlation between complains about blurred vision and D-MPH daily dosage was found.

Conclusions: Our findings provide further support to the effect of stimulants on pupil diameter, as well as on subjective complains about blurred vision in a dose dependent manner.

Intraocular pressure-lowering drugs influence non-pigmented ciliary epithelium derived exosomes uptake by trabecular meshwork cells

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Background: Exosomes are a major constituent of the aqueous humor (AH), which participates in the communication between the non-pigmented ciliary epithelium (NPCE) and the trabecular meshwork (TM) tissues. Exosomes are small lipid bi-layer membranous vesicles, 40-150nm in diameter, secreted by most cell types in culture, carry a net negative surface charge under physiological conditions that can contribute to exosome-exosome interactions, and capable of manipulating cellular functions for the maintenance of biological homeostasis and disease progression, such as in glaucoma disease. Given the lack of knowledge of whether eye drops for glaucoma treatment may contribute to NPCE-TM communication mediated by exosomes, we found it interesting to evaluate the effect of commercial intraocular pressure-lowering drugs on the entry of exosomes by changing their zeta potential (ZP).

Purpose: Our purpose was to investigate the effect of physicochemical properties on exosomes interactions with glaucoma eye drops in the context of the pathway by which exosomes enter the target cells.

Methods: Exosomes were isolated by precipitation method and concentrations were determined by Tunable Resistive Pulse Sensing technology. To evaluate the ionic strength (IS) effects on exosomes size and ZP, different PBS buffer strengths, eye drops solutions used for POAG treatment; Alphagan-P®, V-OPTIC®, AZOPT®, Lumigan®, and Travatan®, their active ingredients; Timolol maleate, Brinzolamide or their preservative benzalkonium chloride were analyzed. The size, ZP, and IS of exosomes were measured using NTA and Zeta sizer devices, respectively. The contribution of exosomes interactions to the internalization ratio, regulated by TM cells, was examined at different time points.

Results: Exosomes size and ZP were affected by the IS of the buffer rather than exosomes type. Commercial glaucoma eye drops including ²-blocker, ²-±-agonist, and prostaglandin analogs, reduced NPCE exosomes ZP. Whereas, exposure of exosomes to carbonic anhydrase inhibitor caused an increase in the ZP. A correlation was found between increased ZP values and increased NPCE exosomes uptake by TM cells. We were able to show that Benzalkonium chloride stands behind this ZP effect and not Timolol or Brinzolamide.

Conclusions: Our findings suggest that exosomes size, surface membrane charge, and IS of the surrounding, have an impact on exosome: exosome interactions which affect the uptake of NPCE exosomes by TM cells.

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Retinal degenerations
Live+VOD

Retinal dystrophy as part of TTC21B-associated ciliopathy

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Purpose: TTC21B is a ciliary protein. The most common phenotypic features associated with TTC21B biallelic mutations are nephronophthisis and skeletal abnormalities. To date, retinal dystrophy has been mentioned very briefly, in only one patient. We provide for the first time detailed ophthalmic phenotype in a patient with TTC21B mutations.

Methods: Clinical evaluation included best-corrected visual acuity, cycloplegic refraction, fundus examination, fundus photography, retinal imaging by optical coherence tomography, full-field electroretinography, multifocal electroretinography and visual evoked potentials. Genetic analysis included Whole Exome Sequencing and confirmation of the identified mutations in the patient and his parents by PCR amplification and direct sequencing.

Results: A ten-year-old white male presented with nephronophthisis, high myopia and nycatalopia. Best-corrected visual acuity was preserved to 20/20 in each eye with significant myopic correction. Visual fields were constricted. Optical coherence tomography confirmed lack of outer retinal layers in the perifoveal area on both eyes. Electroretinography confirmed significant retinal dystrophy. Whole Exome Sequencing revealed compound heterozygous mutations in the TTC21B gene.

Conclusions: TTC21B is associated with ciliopathy, but retinal dystrophy is a rare finding in these patients. We report retinal dystrophy secondary to TTC21B mutations, and provide for the first time detailed clinical information of the ophthalmic exam.

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Cornea
Live+VOD

EndoArt: a synthetic implant for the treatment of corneal edema

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Purpose: To present a novel synthetic plate that can substitute the barrier function of the corneal endothelium and attenuate corneal edema, as a replacement for Endothelial keratoplasty surgeries.

Methods: This is a prospective, open-label, feasibility, multi-center, non-randomized clinical trial, conducted in 6 sites. The primary safety end point of this study was the frequency and severity of all treatment-related adverse events, during and after implantation of the EndoArt and throughout the 6-month follow-up period. The secondary efficacy end points included corneal thickness, corneal clarity, pain (VAS) and Best Corrected Distance Visual Acuity (BCDVA).

Results: 15 consecutive patients, underwent EndoArt implantation. 5 of those patients followed up for mean time of 12.3 months. The remining 10 patients are still in the initial follow up phase (1-3 months). None of the patients had late detachment or complications. Mean initial visual acuity in the involved eye before surgery was 1.99 (0.27 ±,ı) LogMAR, and at the final visit visual acuity improved to 1.31 (0.66 ±,ı) LogMAR. Mean initial corneal thickness in the involved eye before surgery was 796 µm, improving to 599 µm.

Conclusions: the implantation of the EndoArt demonstrated that a synthetic implant attached to the inner cornea can relieve corneal edema. No side effects were observed during 10-15 months of follow up. The EndoArt may provide an alternative to endothelial keratoplasty for the treatment of corneal edema.

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Retina
Live+VOD

Aflibercept Clearance Through the Drainage System in a Rat Model

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Purpose: As intravitreal anti-VEGF injections became the mainstay of treatment for many retinal diseases, the cause of a secondary sustained elevated intraocular pressure is still unclear. The aim of our study was to study the clearance of Aflibercept from the anterior chamber angle, in a rat model, to test if an aggregation exists.

Methods: Choroidal neovascular lesions (CNV) were induced in the right eye of 12 brown Norway rats, using indirect laser ophthalmoscope. Intravitreal Aflibercept injection (0.12mg/3µl) was performed 3 days after CNV induction. Rats were euthanized at predetermine time intervals of 3,6,24 and 48 hours post injection, with immediate enucleation for histological analysis with H&E and immunofluorescence staining.

Results: Immediately after the injection, a strong fluorescence signal was detected, Indicating the presence of Aflibercept in the iridocorneal angle. At 3- and 6-hours interval a strong signal of Aflibercept was still seen. While at 24 hours after the initial injection the intensity of the signal was decreased significantly, at 48 hours there was no fluorescence signal, confirming complete clearance of Aflibercept.

Conclusions: In our rat model, a complete clearance of Aflibercept from the anterior chamber angle, was seen 48 hours after the injection.

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Cornea
VOD

A new method for the attachment of posterior lamellar grafts, leaving no air bubble in the eye

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Purpose: To describe the clinical outcomes of using Viscoat as a tamponade agent for the attachment of the EndoArt® graft in rabbit and pigsâ€™ eyes.

Methods: A total of eight eyes (five rabbit eyes and three pig eyes) were followed up after EndoArt® implantation. The graft was initially attached with air injection, and air-Viscoat exchange was then performed. Viscoat was injected into the anterior chamber, forming tamponade to prevent decentration or detachment of the graft. The Viscoat material located around the pupil, in the anterior chamber and near the angle was then aspirated in most of the eyes. Intraocular pressure was measured before the operation, on post-operative days 1, 8 and 16.

Results: Three rabbit eyes were followed up for 16 days, the rest for eight days. In all eyes, grafts remained attached throughout the follow-up time. No intraocular elevation was seen at any time point.

Conclusions: This study supports the notion that Viscoat is safe and efficient when being used as tamponade agent during posterior lamellar corneal grafts.

Minimally invasive Micro Sclerostomy (MIMS) procedure - a novel filtration procedure for glaucoma treatment

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Purpose: To evaluate the safety, feasibility and efficacy of a novel surgical system, the Minimally Invasive Micro Sclerostomy (MIMS), in an in-vivo porcine experimental model and in glaucoma patients.

Methods: MIMS (Sanoculis Ltd, Israel) is a stent-less filtration procedure. In the first generation of MIMS, in a porcine model, the system included a hand piece with a 600 µm needle, containing an injectable 300 µm triangular blade that spins around its longitudinal axis. The needle was inserted ab-externo into the subconjunctival space with the blade injected at the limbal area, creating a drainage channel connecting the anterior chamber to the sub-conjunctival space. The first generation of MIMS was assessed in a porcine experimental model on 14 pigs. The second generation included a micro-trephine, was performed ab-interno and was tested on 31 glaucoma patients in India. In both experiments the safety and efficacy of MIMS were studied. In the human trial, complete success was defined as an IOP between 5 and 21, with 20% reduction from baseline, without hypotensive medications. Shape and location of the scleral tunnel, the sub-conjunctival bleb and the healing process were examined by biomicroscopy and by AS-OCT. In the porcine model histopathological analysis was also performed.

Results: No device malfunctions nor significant intra or post-operative complications were recorded in both experiments. An open tract was achieved as demonstrated by an AS-OCT. Effective fluid percolation was achieved in all eyes. Mean IOP decreased from 18.7±3.4 mmHg preoperatively to 12.3 ± 3.5mmHg on the first follow-up visit (P<0.001) in the porcine model. In the human trials using the second-generation MIMS, IOP was reduced from 31.2 ±6.9 mmHg preoperatively to 16.4±3.3 and 15.6±2.7 mmHg at 6 and 12 months, respectively. Complete success was achieved in 74% and 57% of glaucoma patients at 6 and 12 months, respectively

Conclusions: MIMS procedure exhibited a consistent and relatively high safety, feasibility and efficacy profiles in both a porcine model and over an intermediate follow up period in glaucoma patients.

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Glaucoma
Live+VOD

Characterization of glaucoma visual field endpoints based on subgroups of points using the Humphrey Field Analyzer and the Compass perimeter

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Purpose: Outcome measures that encompass particular subsets of visual field points may be useful in clinical trials of novel interventions in glaucoma. We propose and characterize several such outcome measures and compare them as obtained with Humphrey (HVF) and Compass perimeters.

Methods: 30 subjects with glaucomatous neuropathy performed a pair or 24-2 tests with each of 2 perimeters, HVF and Compass. Mean deviations (MD) and their standard deviation (SD) were calculated by averaging total deviation values in the whole field and separate vertical hemifields, and the. Indices were recalculated after censoring of points with low sensitivity (MDc), and then including only points with total deviation probability of <5% (MDc5%) or <2% (MDc2%). Test-retest variability was assessed using Bland-Altman 95% limits of agreement (95%LoA).

Results: For the whole field, using HVF, MD was -7 .5 ± 6.9 dB, MDc -3.6 ± 2.8 dB, MDc5% -6.4 ± 1.7 dB and MDc2% -7.3 ± 1.5 dB. With Compass MD was -7.5 ± 6.6, MDc -2.9 ± 1.7 dB, MDc5% -6.3 ± 1.5, and MDC2% -7.9 ± 1.6. The respective 95% LoA were 5.5, 5.3, 4.6 and 5.6 with HVF, and 4.8, 3.7, 7.1 and 7.1 with Compass. The respective number of eligible points were 52, 42 ± 12, 20 ± 11 and 15 ± 9 with HVF, and 52, 41.2 ± 12.6, 10 ± 7 and 7 ± 5 with Compass. With both machined, SD and 95%LoA increased in hemifields compared to the total field, but this increase was mitigated after censoring.

Conclusions: Restricting analysis to particular subsets of points in the visual field can provide outcome measures with a range of mean deviation, a markedly reduced SD and therefore more homogenous dataset, and in many cases better test-retest variability. Increasing restriction results in progressively fewer points available for analysis. Investigators can use such outcome measures to increase the sensitivity of glaucoma clinical trials.

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Retina
Live+VOD

Intravitreal Tissue Plasminogen Activator Injection for the Treatment of Proliferative Vitreoretinopathy in a Rabbit Model

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Purpose: To evaluate the effect of intravitreal injection of tissue plasminogen activator (tPA) on proliferative vitreoretinopathy (PVR).

Methods: Experimental PVR was induced in the right eye of rabbits by intraocular injection of dispase (0.05 U/0.1 mL). Progression of PVR was followed by indirect ophthalmic examination. Six weeks after Dispase injection, animals were divided to receive intravitreal injection of either 25 µg/0.1 mL tPA or balanced salt solution (BSS). Animals were euthanized at 48 hours following tPA/BSS injection and eyes were enucleated for histological evaluation. Immunostaining for fibroblasts using Mouse Monoclonal anti Rabbit ¯±-smooth muscle actin (¯±SMA) and staining for collagen using Sirius Red were performed.

Results: Five PVR model eyes were injected with tPA and four with BSS. Following tPA injection, one eye had a reduction in PVR from grade 2 to 1, three eyes remained stable and in one eye the severity of PVR couldn't be assessed due to limited vision. In the BSS group, PVR grade was unchanged in three eyes and couldn't be visualized in one eye. Staining of histological specimens with ¯±SMA showed a reduced presence of fibroblasts in eyes injected with tPA compared with BSS. In addition, collagen, demonstrated by Sirius Red staining, was reduced in the tPA group in comparison to controls.

Conclusions: Our results suggest that intravitreally injected tPA may show an inhibitory effect on PVR progression. This experiment provides a scientific rationale for further exploration of the use of intravitreal tPA for the treatment of PVR in clinical trials.

IOL power calculation using the Kane formula in comparison to existing methods in the elderly population

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PURPOSE: To assess the accuracy of the Kane formula for intraocular lens (IOL) power calculation in comparison to established formulas in the elderly population.

METHODS: Retrospective data from 90 patients ≥75 years old who underwent uneventful cataract surgery with SN60WF IOL implantation were evaluated. The first operated eyes of patients with final best-corrected visual acuity 20/40 or better and axial length 22-26 mm were included. Prediction errors were calculated for Barrett Universal II (BUII), Haigis, Hoffer Q, Holladay 1, Kane and SRK/T formulas. A subgroup analysis based on age (75-84 and ≥85 years old) was performed.

RESULTS: Use of both BUII and Kane formulas resulted in the highest percentage of eyes with prediction errors within ±0.50 D (72% each) and significantly higher than Hoffer Q, Holladay 1 and SRK/T (p=0.001). Rates of predictability within ±0.25 D and ±1.00 D were 31%-38% and 87%-92%, respectively, with no significant differences between formulas. No statistically significant difference was seen between formulas in the median absolute error. These tendencies remained consistent in both age groups when analyzed separately. Subgroup analysis showed better predictability of all formulas in the younger age group.

CONCLUSION: This is the first study evaluating the Kane formula exclusively in the elderly population. The Kane formula was found to be of equal accuracy to the BUII and superior to the Hoffer Q, Holladay 1 and SRK/T formulas. Very elderly patients may have reduced refractive precision using all formulas.

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Cataract
VOD

Visual outcomes of an extended depth of focus intraocular lens in patients with retinal pathologies compared to healthy eyes

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Purpose: To evaluate the visual outcomes and patientsג€™ satisfaction following cataract extraction surgery with implantation of an extended depth of focus (EDOF) intraocular lens (IOL) in patients with retinal pathologies and healthy eyes.

Methods: Twenty-five eyes with retinal pathologies and 100 healthy eyes that underwent cataract extraction with implantation of an EDOF IOL and had at least 3 weeks postoperative follow up were included. Visual outcomes were reviewed from patients' charts. Patients' overall satisfaction, spectacle dependence, visual perception and side effects were evaluated with a self-reported questionnaire.

Results: Mean uncorrected visual acuities (LogMAR) were significantly better in the healthy eyes compared with retinal pathologies: 0.05 and 0.11, p=0.02 (distance), 0.06 and 0.15, p=0.02 (intermediate) and 0.20 and 0.30, p=0.02 (near), respectively. Forty-six (70.7%) and 9 (47.4%) patients, respectively, reported no or rare use of spectacles for any distance (p=0.06). Haloes/glare were reported by 11 (16.9%) and 5 (26.4%) patients, respectively, "often" or "all the time" (p=0.343); only 4 (7.4%) and 1 (5.6%) patients reported that it disturbs them "often" or "all the time" (p>0.99). Fifty (76.9%) and 13 (68.4%) patients, respectively, declare that they would choose the same IOL again (p=0.55).

Conclusion: Eyes with retinal pathologies that were implanted with an EDOF IOL demonstrated excellent distant and intermediate uncorrected visual results with reasonable near uncorrected visual results; however, results were inferior to those of control healthy eyes. Patient satisfaction was high despite some report of glare and haloes.

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Cornea
Live+VOD

Keratoplasty for keratoconus in young patients: demographics, clinical features and post-transplant outcomes.

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Purpose: To examine pre-transplant findings and outcomes of corneal transplants for keratoconus in children.

Methods: This is a retrospective cohort (national registry) study. Data on all patients (n = 161) aged 16 or younger who had a first graft for keratoconus between 2003 and 2017 in all corneal transplant centers in the UK were examined. The influence of demographic variables, pre-transplant corneal findings and transplant type on two-year outcome was examined. Graft and rejection-free survival and visual acuity were compared with adults aged 17-25 (n = 1986) and >25 years (n = 4763) who had first grafts for keratoconus.

Results: Children had poorer pre-transplant visual acuity, higher rates of corneal vascularization and ocular surface disease than adults. However two-year post-transplant corrected visual acuity reached 20/20 or better in a higher proportion of children (35%) than in young (30%) or older (28%) adults. Graft failure and rejection rates were lower for children up to 16 years, 3% ($p = 0.619$) and 11% ($p = 0.197$) respectively, compared to adults. Irreversible rejection was not recorded for any transplant in a child. Analysis for influence of age on differences in 2-year graft and rejection-free survival in childhood and adult groups by Kaplan-Meier and Cox regression methods indicated non-significant effects. Children whose procedure was a DALK had lower graft rejection-free estimates than for PK ($p = 0.13$) but no difference in survival.

Conclusions: Young keratoconus patients have excellent transplant outcomes and visual results. In keratoconus with poor corrected acuity in a young patient, in this large cohort there is no evidence of outcome advantage in delaying transplantation.

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Cornea
Live+VOD

The Toxicity of Eye Drops for Dry Eye Disease on In Vitro Models of Corneal Epithelium

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Purpose: The armamentarium of eye drops for the treatment of dry eye disease is wide. As patients often report adverse effects of burning sensation and clinical signs reveal corneal epithelial cells toxicity, we aimed to evaluate, in vitro, which of the three commonly prescribed dry eye medications, Tacrolimus, Lifitegrast and Cyclosporine, is more toxic to the ocular surface.

Methods: Primary and immortalized human corneal epithelial cells were seeded on 96 wells and treated with 20% of tested drug and 80% medium when they reached full confluence. After applying the treatments for either 30 seconds, one minute, one hour and four hours, cells were rinsed twice with PBS and medium was replaced. Bright field images and XTT cell proliferation kit were analyzed 72 hours after the initiation of treatments. Five repeats were performed for each tested drug in the four time exposures. Statistical analysis performed by Wilcoxon followed by Steel method comparison with saline as control.

Results: Cells viability was significantly impaired on immortalized cells following 30 seconds treatment with Tacrolimus 0.03% (3%, p=0.015%) and Tacrolimus 0.1% (3%, p=0.006%). While on primary cell cultures, cells viability was significantly altered after one-hour treatment with Tacrolimus 0.1% (8%, p=0.043%) and four hours treatment with Tacrolimus 0.03% (17%, p=0.042%). Lifitegrast decreased cells viability after one-hour treatment on immortalized cells (1%, p=0.006), and after four hours on primary cells (10%, p= 0.042). Interestingly, Cells viability on both primary and immortalized corneal epithelial cells was not altered following Cyclosporine treatment compared to Saline, and even a significantly higher cells viability was noted on immortalized cells treated with Cyclosporine for one hour (111%, p=0.016). Imaging for cells morphology after each treatment supported the stated results and further experiments showed drugs toxicity was dependent on time exposure to each drug as well as its concentration.

Conclusions: Our results demonstrate highest toxicity of Tacrolimus to the corneal epithelium in both primary and immortalized cell cultures, while Cyclosporine proved most protective to epithelial cells in vitro.

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Oculoplastics
Live+VOD

Long-term outcomes after multidisciplinary treatment for pediatric orbital rhabdomyosarcoma

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Purpose:

To describe the clinical presentation, imaging characteristics, prognostic factors, and treatment outcomes of pediatric orbital rhabdomyosarcomas (RMS).

Methods: We designed an institutional retrospective study with data from 42 patients with primary RMS of the orbit treated between 1995 and 2016 at our center. We evaluated demographic characteristics, symptoms and signs, imaging characteristics, risk factors and treatment outcomes.

Results: The mean age at presentation was 7.8 years (range, 9 months to 16 years) with a median of 7 years. The mean follow-up was 10.62 years (median, 9.43; range, 3 to 30 years). Eyelid swelling (in 45% of cases) was the most common presenting manifestation. Half the patients (21/42) underwent macroscopical tumor excision and brachytherapy as a part of the (full) AMORE protocol, 4 patients were treated locally using a proton beam, 5 were treated locally using EBRT, and 12 were treated using chemotherapy alone.

We found 15 cases with recurrences, 10 of them underwent exenteration and two died. Histologically all cases had embryonal RMS except two alveolar cases with PAX3 positivity in immunohistochemistry.
The 10-year overall survival was 93.6%. All non-exenterated patients had functional visual acuity (>0.5). Cataract was the most common (32%) adverse event of local treatments, 3 cases underwent cataract removal surgery, and all cataract cases had functional visual acuity.

Conclusions: Orbital RMS in this series presented a 10-year survival rate of 93.6%, and 31 patients had functional vision at the time of follow up. Intraconal apical involvement with lacrimal gland and pre-septal invasion may decrease the event-free survival rate.

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Pediatrics
Live+VOD

Long term follow up of functional and structural findings in infants treated for retinopathy of prematurity, using OCT angiography

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Purpose: Retinopathy of prematurity (ROP) is a vasoproliferative retinopathy of preterm infants and a leading cause of permanent blindness and visual impairment. It is characterized by abnormal retinal vascular development and therefore, in advanced stages, laser photocoagulation is indicated. Optical coherence tomography angiography (OCTA) is a non-invasive tool that uses motion contrast to study different levels of retinal vasculature. In this study we wish to assess the foveal microvascular structure of children with ROP treated with diode laser photocoagulation (DLP), using OCTA.

Methods: The study group included 11 children (18 eyes) aged 9-16 years who were born at <32 weeks, weighing <1200g, and underwent DLP for ROP (stage 3 in 15 eyes, stage 2 in 1 eye, no data in 2 eyes). The control group comprised 12 healthy age-matched children (23 eyes) born at term. Participants underwent full ophthalmologic examination followed by OCTA (RTVue XR 100 Optovue). Findings for foveal avascular zone (FAZ) area, vascular and flow density, and central macular thickness were compared between the groups and correlated with gestational age, birth weight, refractive status and intraventricular hemorrhage (IVH).

Results: Compared with the controls, the ROP group had a smaller FAZ area ($P<0.001$), lower deep vascular plexus density ($P<0.001$), lower flow density ($P=0.025$), and greater central macular thickness ($P<0.001$). IVH at birth correlated with FAZ area ($P=0.026$) and inner macular thickness ($P=0.011$); IVH grade 2 was associated with the thickest macular layers, and IVH grade 1 with the thinnest.

Conclusions: Using OCTA, we were able to identify significant quantifiable long-term macular microvascular and structural changes in this patient population.

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Retina
VOD

Bilateral Torpedo Maculopathy in a Neonate with Congenital Cytomegalovirus Infection

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Background: Torpedo Maculopathy is a rare congenital abnormality that presents with a torpedo-like macular hypopigmented lesion of the RPE. The typical presentation is an asymptomatic unilateral incidental flat oval lesion localized temporal to the fovea with a distinctive tip pointing towards the fovea. This condition has not been associated with any systemic or ocular abnormalities. The diagnosis of Torpedo Maculopathy is clinical, based upon recognition of its unique fundoscopic characteristics. Visual field losses have previously been described, but it is predominantly a benign non-progressive finding, so no treatment is required. The exact pathophysiology is yet to be revealed, but it is thought to be the sequella of a congenital malformation occuring during intrauterine fetal development.

Methods: We present a case of a 3-weeks-old neonate who was hospitalized due to failure to thrive and poor feeding. His pregnancy was complicated with intrauterine growth retardation. Comprehensive investigation yielded positive urine samples for cytomegalovirus, indicating congenital infection. Brain MRI demonstrated pontocerebellar hypoplasia. The ophthalmic examination revealed bilateral flat, ovoid, hypo-pigmented atrophic lesions located temporally to the fovea, more prominent in his right eye. The anterior segments were normal, and other ocular abnormalities were not found. A diagnosis of congenital CMV infection with active retinitis OU was established, and he was started on intravenous anti-viral treatment. During his follow up, these lesions did not change.

Results: Based on the fundoscopic findings, a diagnosis of bilateral Torpedo Maculopathy was established, and the anti-viral treatment was discontinued, as well as the frequent follow-ups for presumed active CMV retinitis.

Conclusion: To our best knowledge, this is the first report of bilateral torpedo maculopathy in a neonate. The question remains whether intrauterine CMV infection possibly triggered a cascade leading to developmental malformations resulting in pontocerebellar hypoplasia and the typical torpedo-like lesions. Recognizing the typical findings in this rare condition may help us provide better care for our patients and save them unnecessary investigation and treatment.

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Genetics
Live+VOD

The thin line between syndromic and non-syndromic inherited retinal dystrophy

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Purpose: To identify the genetic basis for inherited retinal dystrophy (IRD) in two Israeli families.

Methods: Clinical evaluation included best-corrected visual acuity, fundus examination and full-field electroretinography. Genetic analysis included Whole Exome Sequencing and confirmation of the identified mutations by PCR amplification and direct sequencing.

Results: A patient with the combination of retinitis pigmentosa (RP) and neurosensory hearing loss (NSHL) was initially diagnosed with Usher syndrome. The patient was eventually found to be compound heterozygous for two missense mutations in the BBS2 gene (p.Asp104Ala and p.Gly81Cys), which is associated with Bardet-Biedl Syndrome or with non-syndromic RP, both autosomal recessively inherited. In addition, the patient was heterozygous for a rare and presumably pathogenic mutation in the PAX3 gene (p.Ile188Leu), associated with Waardenburg Syndrome, a form of syndromic NSHL which is inherited as autosomal dominant with partial penetrance. A second patient, diagnosed with non-syndromic isolated retinal dystrophy, was found to be homozygous for a PEX6 mutation, previously associated with Zellweger Syndrome or with Heimler Syndrome. This hypomorphic mutation (p.Arg601Gln) was not previously reported in homozygosity.

Conclusions: IRDs, which are among the most common genetic diseases in humans, define a clinically and genetically heterogeneous group of disorders. While in most cases of IRD the disease is limited to the eye (non-syndromic), over 70 forms of syndromic IRDs have been described. The common working paradigm for the ophthalmologist is combining the different symptoms observed in a patient to one unifying diagnosis; Nevertheless, since IRD is a strikingly heterogeneous condition, it may coincide with other genetic (and non-genetic) rare conditions. On the other hand, hypomorphic alleles of genes underlying syndromic IRD may be associated with non-syndromic IRD. Due to the high degree of phenotypic variability and phenotypic overlap found in IRD, correct diagnosis based on phenotypic features alone may be challenging and sometimes misleading. Therefore, genetic testing is the benchmark for the diagnosis and management of patients with these conditions, as it complements the clinical findings and facilitates an accurate clinical diagnosis and treatment.

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Anterior segment
Live+VOD

Acoustic Manipulation of Intraocular Particles

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PURPOSE: To describe a novel noninvasive method for manipulating intraocular particles by means of acoustic manipulation.

METHODS: A type-II piezoelectric cylinder was used as an acoustic resonator to form standing acoustic waves at a frequency of 1.1±0.1 MHz. In-vitro and ex-vivo (porcine eyes) models were used to evaluate the safety and feasibility of the technique in manipulating intraocular particles. Two types of particles were used: triamcinolone acetonide (TA) and porcine iris pigment.

RESULTS: Upon activation of the acoustic wave in the in-vitro model, the particles became rearranged into concentric rings. The ring patterns formed in the cylindrical resonator corresponded with the node areas of a standing acoustic wave. Stronger acoustic fields (higher amplitudes) resulted in narrower rings. Six additional porcine eyes were used for safety evaluation, and no macroscopic, microscopic, or histologic signs of tissue damage were observed. Both the pigment and TA particles within the anterior chamber became rearranged into concentric rings in a similar fashion to that observed in-vitro.

CONCLUSIONS: Our study introduces a novel noninvasive method for manipulating intraocular particles using acoustic manipulation. The method was proven to be safe and feasible in in-vitro and ex-vivo models, and has the clinical potential for moderating or preventing injury resulting from accumulation and dispersion of particulate matter in the eye.

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Oncology
VOD

Lag time between onset of symptoms and treatment of retinoblastoma: an international collaborative study of 692 patients from 10 countries

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Purpose: To determine lag time between onset of symptoms and diagnosis of retinoblastoma (RB) in countries based on their national-income and analyze its effect on the outcomes

Methods: Prospective interventional case series from 11 treatment centers in 10 countries

Results: Of the 692 patients, 74 (11%) were from low-income country (LIC) (Ethiopia), 294 (42%) from lower middle-income countries (LMIC) (Bangladesh, India, and Pakistan), 254 (37%) from upper middle-income countries (UMIC) (China, Peru, and Russia), and 70 (10%) from high-income countries (HIC) (France, UK, and USA). The following factors were significantly different among different countries, LIC vs LMIC vs UMIC vs HIC: age at diagnosis (months) of RB (31 vs 24 vs 22 vs 21; p=0.001), distance from home to nearest health care center (miles) (34 vs 24 vs 47 vs 10; p=0.03), and mean lag time between detection of first symptom to visit to RB treatment center (days) (303 vs 180 vs 92 vs 56; p=0.0007). The factors influencing increased lag time between onset of symptoms and diagnosis of RB included lower-national income level (p<0.001), increased number of visits to primary health care centers (p<0.001), increased distance from home to RB treatment center (p=0.02), strabismus as the first symptom of RB (p=0.001), and increasing age (p<0.001). The significant differences in the tumor characteristics and outcomes between LIC vs LMIC vs UMIC vs HIC included T1 tumor (20% vs 11% vs 13% vs 24%; p=0.006), T4 tumor (20% vs 9% vs 7% vs 0%; p=0.0004), lymph node metastasis (19% vs 2% vs <1% vs 0%; p<0.0001), and globe salvage (30% vs 60% vs 65% vs 68%; p<0.0001). After adjusting for country income, increased lag time between onset of symptoms and diagnosis of RB was associated with higher chances of an advanced tumor at presentation (p<0.001), higher chances of high-risk histopathology features (p=0.003), regional lymph node metastasis (p<0.001), systemic metastasis (p<0.001), and death (p<0.001).

Conclusion: There is a significant difference in the lag time between onset of symptoms and referral to a RB treatment center among countries based on national-income resulting in significant differences in the presenting features and clinical outcomes. Decreased lag time and an early diagnosis of RB is desired to lower the chances of high-risk histopathologic features, metastases, and death.

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Cornea
VOD

Comparison of serological characteristics of Sjogren's syndrome and dry eye syndrome patients using a novel immune serology technique

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Purpose: To compare hematologic and serological parameters among patients with Sjogrenג€™s syndrome (SS), dry eye syndrome (DES) and controls, and validate a novel multiplex-serology method for identifying auto-antibodies in these populations.

Methods: In a clinic-based case-control study a total of 422 participants were recruited, including 91 with SS, 120 DES, and 211 controls (age and sex frequency-matched). We measured blood counts, anti-nuclear-antibodies (ANA), anti-SSA/SSB, anti-ribonucleoprotein (RNP), anti-double-stranded-DNA (DS-DNA), and rheumatoid factor (RF) using the ג€œImmunodotג€• qualitative-ELISA assay. Immunoglobulins, C3 and C4 were measured by immune-fluorescence. Autoantibodies were also quantified with a newly-developed method using glutathione-S-transferase fusion proteins of SSA/Ro 52 and 60kD and SSB/La (multiplex-serology), measuring median fluorescence intensity (MFI).

Results: Among DES patients, only 2% (95%CI: 0.36-6.3) had positive immune serology. SS patients had lower lymphocyte, hemoglobin and C3 levels but higher prevalence of RF, ANA, anti-SSA/B and higher IgG and MFI levels, compared to DES and controls (P<0.001). Presence of anti-SSA/Ro-52kD was associated with SS [odds ratio (OR)=2.05, 95% confidence interval (CI): 1.46-2.88]. Anti-SSB/La was inversely associated with DES (OR=0.81, 95%CI: 0.65-1.00) compared to controls. Positivity to RF (adjusted for age, gender and ethnicity OR=5.03, 95%CI: 1.78-14.21), ANA (OR=14.75, 95%CI: 4.09-53.17), or combination of anti-SSA/B (OR=20.97, 95%CI: 4.60-95.54) were more likely in SS compared to DES. The novel multiplex-serology method correctly identified anti-SSA/B autoantibodies by ELISA among SS, DES patients and controls (sensitivity=1.0, negative-predictive-value=1).

Conclusions: Serologic parameters distinguish SS from DES patients and controls. A newly-developed multiplex-serology technique may be useful to detect autoantibodies in large epidemiologic studies.

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Pediatrics
VOD

Overaction of the IO Muscle as the Effect of Extorted Eye Movement Paths on Two Normal Eye Movements, Not Representing True Overaction after All

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Introduction: Weiss and later Guyton suggested that "overaction" of the inferior oblique muscles is not caused by increased tonus of the inferior oblique muscles on adduction but rather simply mechanically from the phenomenon that Guyton termed "sensory extorsion". When there is a defect in binocular vision, the inferior oblique muscles can shorten, with accompanying lengthening of the superior oblique muscles, from unguided muscle length adaptation, holding both eyes in abnormally extorted positions. On side gazes, the non-fixing eye travels upward along its extorted eye movement path, accentuated by a vertical version keeping the fixing eye level, requiring no abnormal increase in inferior oblique tonus.

Methods: We retrospectively studied Lancaster Red-Green plots of patients with inferior oblique muscle "overaction", before and after monocular occlusion for 30 to 60 minutes. Objective torsion and fusion status were also recorded.

Results: After a patch test in patients with central fusion, the non-fixing eye's movement path became more linear.

Discussion: Kushner argued that true overaction of the oblique muscles is present in these patients, as he described curvilinear eye movement paths on side gazes. But in our patients who could fuse centrally, the eye movement paths became more linear after patch testing, favoring the more mechanical explanation.

Conclusion: The illustrated cases support our hypothesis that short inferior oblique muscles simply hold the globes in extorted positions, and the apparent inferior oblique muscle "overaction" is simply from the eyes following their rotated movement paths on side gazes, not from abnormally increased tonicity in adduction.

A novel biomarker for adverse outcome in high-risk pregnancy: OCT-measured thinning of specific retinal layers

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Purpose: To determine whether specific retinal layers are associated with adverse outcome in high-risk pregnancies.

Methods: This prospective observational study included 32 pregnant women (64 eyes), 15 of whom were defined as high-risk (including gestational hypertension complications). We performed swept-source OCT macular examinations and measured selective layers. Clinical data were gathered, with attention on adverse obstetrical outcome defined as any of the following: preterm delivery, pre eclampsia, pregnancy induced hypertension, elevated liver function tests, thrombocytopenia and need for magnesium to treat severe pre-eclampsia.

Results: The group defined by any adverse outcome comprised 17 patients (34 eyes, 53%). Inner superior (P=0.04) and inferior (P = 0.09) ganglion cell layers were thinner in patients experiencing adverse obstetrical outcomes. This association was retrieved when considering all inner superior (P=0.03) and inferior retinal layers (P=0.03) as well as total macular volume (P=0.02).

Conclusions: The macular ganglion cell layer could be used as a biomarker in pregnancy, specific thinning of this layer being associated with adverse pregnancy outcome.

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Anterior segment
VOD

Predicting factors for the efficacy of cross-linking for keratoconus

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Purpose: To evaluate success predictors in corneal cross-linking (CXL) for keratoconus in a large cohort and extended follow-up.

Methods: A retrospective study based on a prospectively built database Participants underwent CXL for keratoconus from 2007 to 2018 with at least 1-year follow-up. We analyzed effects of CXL type (Epithelium-on or Epi-off and Accelerated or Non-Accelerated) and preoperative factors including age, gender, baseline LogMAR visual acuity (LogMARpre), maximal corneal curvature (Kmaxpre), pachymetry, refractive and topographic cylinders, spherical equivalent (SEpre), mean corneal curvature (MeanK) and follow-up time on outcome measures. The outcome measures were the final change of Kmax (Delta Kmax = Kmaxlast – Kmaxpre) and the final change in LogMAR visual acuity (Delta LogMAR = LogMARlast – LogMARpre).

Results: 613 eyes from 456 patients were included. Mean Kmax decreased from 54.07 diopters to 52.84 diopters ($p<0.001$) over five years. Mean LogMAR decreased from 0.28 to 0.25 ($p<0.001$) over 3 years. multivariate analysis showed four factors associated with negative Delta Kmax: high Kmaxpre, high SEpre, low MeanKpre, and non-accelerated procedure.

Multivariate analysis showed three factors associated with negative Delta LogMAR: high LogMARpre, high SEpre, and Low MeanKpre.

Conclusion: CXL for keratoconus is a highly effective treatment, as evident by its effects on the outcome measures: Delta Kmax and Delta LogMAR. High Kmaxpre, high SEpre, and high LogMARpre express a severe disease, and simultaneously, also predict success in CXL. The non-accelerated protocol was associated with successful outcomes, as well. Low MeanKpre also predicts CXL success, although it usually reflects a less severe disease.

IOL Power calculation in irregular corneas, employing Scheimpflug derived central 2mm spherical equivalent keratometry values.

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Here we present our approach of using Scheimpflug derived central 2 mm keratometry values for IOL calculation.

Methods: Retrospective review of all subjects who underwent cataract surgery in the Bristol Eye hospital using the Holladay analysis of Scheimpflug images of the anterior and posterior corneal surfaces, in the central 2 mm. We used these equivalent keratometry readings (EKR) for SRK/T IOL calculation between 2011 and 2020. The accuracy of our central 2 mm EKR method was evaluated through the calculation of the prediction error (PE) and absolute PE (APE). In addition, percentages of eyes within PE of±0.5, ±1.0D to ±3.0, percentage of subjects achieving vision of 6/6, <6/9, and <6/12, were also analyzed.

Results: This study included 35 eyes of 32 patients. (mean age 60.8±15.6, 54.2% male, Kmax 55.5±7.6, Diopter). Following surgery, visual acuity significantly improved (UCVA: from 1.2±0.48, logMar to 0.66 ±0.45, logMar, p<0.01; BCVA: from 0.59±0.48, logMar to 0.25±0.24, logMar, p<0.01). The PE was -0.27±1.6, and the APE was median 0.70 (interquartile range: 2.01). Percentage of subjects with 6/6, <6/9 and <6/12 was 14.3%, 54.3% and 65.7% respectively. Percentage of subjects with PE of±0.5, ±1.0, ±1.5, ±2.0, 2.5D and ±3.0 was 31.4%, 62.9%, 68.6%, 73.3%,85.7% and 88.6% respectively.

Conclusions: Using the Scheimpflug central 2mm EKR for IOL calculation in irregular corneas results in an accurate prediction of actual postoperative refraction. This method may be used in cases where IOLMaster is not able to provide a reliable reading in abnormal corneas.

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Neuro-ophthalmology
VOD

A Retrospective Study to Determine the Normal Range of Vascular Compression of the Optic Nerve and Chiasm

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Background: There is literature to suggest that conditions such as normal tension glaucoma and chiasmatic disorders may be caused by mass effect of blood vessels on the optic nerves or chiasm. We sought to determine whether vascular compression of the optic nerve or chiasm can be an anatomic variant.

Methods: We retrospectively reviewed consecutive 3T head MRI studies performed for any purpose at Hadassah Medical Center. Studies were excluded if there was motion artifact, if they were conducted with a short protocol, or if there was known pathology in the area of the optic nerves, chiasm, or orbit. We then reviewed MRI studies of patients that had undergone a full neuro-ophthalmology examination, where the possibility of an optic neuropathy for a given eye had already been ruled out.

Results: Fifty-four studies of separate patients were included in this study. Twenty-two patients demonstrated vascular compression of the optic nerve by the ophthalmic artery. Of these 22 patients, the ophthalmic artery compression was present bilaterally in three patients and three others had vascular compression at the chiasm. One patient had only vascular compression of the chiasm, and another patient only had vascular compression from the internal carotid artery. The presence of vascular compression was not associated with age, gender, or cardiovascular risk factors. Another eleven patients had undergone a full neuro-ophthalmology exam and had MRI studies that met the inclusion criteria. Of the 17 eyes included, ten demonstrated vascular compression of the optic nerve with no signs of optic neuropathy.

Conclusions: Vascular compression of the optic nerves and chiasm is likely a normal anatomic variant and should not be interpreted as a definitive etiology of vision loss.

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Retina
Live+VOD

Co-culture of hypoxic organotypic retina with adipose derived mesenchymal stem cells ג€“ evaluating the regenerative effect

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Purpose: Ischemia-associated retinal degeneration is a significant cause of vision loss, with currently no effective treatment options. Mesenchymal stem cells (MSC's) are multipotent stem cells that may attenuate neuronal death, have antioxidant features and neurotropic characteristics. The aim of this study was to examine whether ischemic retinal ganglion cells (RGC's) will be salvaged from apoptosis by co-culture of adipose-derived mesenchymal stem cells (ADSC's) by either direct contact or by paracrine activity. In addition we examined the cytokine secretion profile of ADSC's and demonstrated the paracrine effect of ADSC's on ischemic retina by analysing the protein expression in ADSC's conditioned medium.

Methods: Retinas of wild type C57Bl/6 mice were harvested. Deprived of arterial O2 supply, retinas were cultured as an ex vivo organotypic cultures on an insert membrane. The therapeutic potential of ADSC's on ischemic retina was evaluated either by direct contact (ADSC's seeded above the retina) - or by paracrine activity (ADSC's seeded below the retina) (n=16). Retinas were flat-mounted and the number of surviving RGC's was assessed by Brn-3a staining and confocal microscopy.

Results: The number of surviving RGC's was significantly higher in treatment groups compared to controls; Positive Brn-3a cells seeded above the retina= 29 ±10.9, ($p<0.001$), positive Brn-3a cells seeded below the retina= 29 ±7.2, ($P=0.001$), control T48 = 4.5 ±2.5SD. When comparing T0 to treatment groups we did not witness a new RGC's produced, (T0= 23 ±4.6, $P=0.377$).

Conclusions: Our results prove that ADSC's transplantation significantly improved recovery of the RGC's in the ischemic retina. The effect was similar when ADSC's were seeded on top and below the retina. This population of stem cells could serve future development of autologous cell therapy modalities to ischemic retinal and/or optic nerve damage.

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Retina
VOD

Macular neovascularization characteristics in chronic central serous chorioretinopathy patients using Optical Coherence Tomography Angiography

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Purpose: To study the morphological characteristics of type 1 macular neovascularization (MNV) in eyes with chronic central serous chorioretinopathy (CSCR) using optical coherence tomography (OCT) and OCT angiography (OCTA).

Methods: Patients with chronic CSCR and secondary type 1 MNV were included. Macular OCT and OCTA images were acquired. Morphologic characteristics and quantifiable features, measured using Imagej© software, were analyzed.

Results: Twenty eyes of 19 patients were included. All eyes exhibited neovascular flow signal on OCTA images. Nineteen (95%) of eyes showed flat-irregular pigment epithelium detachment (FIPED). Subretinal fluid was detected in 90% of patients with no intra-retinal fluid. Membranes were mostly located at the subfoveal area (65%). All membranes were identified in the location overlying choroidal pachyvessels. Mature membranes with a loose vascular configuration were identified in 75% of eyes. Morphological biomarkers of ג€œindistinct65%) €ג), ג€œtangledג€• (30%) and ג€œsea-fanג€• (5%) patterns were recorded. Feeder vessel was identified in 75% of membranes. Vascular density was measured 46% (± 10%).

Conclusion: Neovascular membrane of chronic CSCR sprout under the retinal pigment epithelium within the macular area (type 1 MNV) inside a FIPED overlying pachyvessels. Morphologic characteristics assessed by OCTA of loose and indistinct pattern improve our understanding of vessel formation and maturation in chronic CSCR patients and might be valuable to guide therapy.

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Retina
Live+VOD

Macular Optical Coherence Tomography Angiography and Fractal Dimension Analysis After Successful Rhegmatogenous Retinal Detachment Repair

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Purpose: Rhegmatogenous retinal detachment (RRD) may cause significant visual loss. Optical coherence tomography angiography (OCTA) provides layer-specific imaging of the retinal blood flow. We describe macular OCTA findings of macula-on and macula-off RRD patients that underwent vitrectomy for RRD repair.

Methods: Consecutive patients who underwent primary 23 or 25-gauge vitrectomy for RRD repair with anatomic success were investigated retrospectively. Best-corrected visual acuity (BCVA), OCT and OCTA were performed. A 3X3 mm2 area, centered on the fovea, was scanned for all study and fellow eyes. Automated segmentation allowed separate analysis of both superficial capillary plexus (SCP) and deep capillary plexus (DCP). For the obtained images, foveal avascular zone (FAZ) area, vessel density and fractal dimension (FD) measurements were computed.

Results: Twenty-two eyes of 22 patients with an average age of 61.14♀± 9.52 years were included, with half (11) of the patients having macula-on RRD. Deep vessel density was significantly lower in macula-off RRD eyes than fellow eyes (464.32 ±♀ % vs 50.747.7 ±♀ %, p=0.047). In both macula-on and macula-off patients, superficial and deep FD measurements were lower in study eyes than fellow eyes (p<0.046).

Conclusions: OCTA provided depth resolved information of the retinal blood flow with the level of detail exceeding previous forms of imaging. Our study has provided, for the first time, FD analysis data that was significantly lower also in eyes after macula-on RRD repair.

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Pediatric
Live+VOD

Correlating environmental and behavioral factors with refractive error in Israeli boys

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Purpose: To assess factors that may influence myopia in three cohorts of Jewish boys with different educational demands.

Methods: Healthy ultra-Orthodox, religious, and secular Jewish boys (n = 36), ages 8-10, were recruited. Refractive status, education, time spent reading and writing, and electronic device use were assessed using a questionnaire, and time outdoors and physical activity were assessed objectively using an Actiwatch Spectrum. Data were analyzed with Chi-Square and Kruskal-Wallis tests, repeated measures ANOVA, and Bonferroni post hoc comparisons.

Results: Ultra-Orthodox (n = 14) and religious (n = 13) children had greater myopia prevalence compared to secular children (n = 9; P = .01), despite no differences in parental myopia. Actigraph data showed that there were no differences in activity (P = .52) or time spent outdoors (P = .48) between groups, although timing of behaviors was different.

Ultra-Orthodox children learned to read at a younger age and spent more hours at school (P < .001 for both). All groups engaged in a similar amount of near work while not in school (P = .52). However, ultra-Orthodox boys had less electronic device use than both religious (P = 0.007) and secular children (P < .001).

Conclusions: This pilot study demonstrates that ultra-Orthodox, religious, and secular children have distinct educational demands, but similar time outdoors, physical activity, and near work while not in school. Findings suggest that near work at school may contribute to previously reported differences in refractive error between groups. However, conclusions should be confirmed in a larger sample size.

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Cornea
VOD

Conjunctival cultures in intensive care unit patients treated for exposure keratopathy

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Background: The normal conjunctival flora has an important role in maintaining ocular surface homeostasis. The very same flora can be the source of infection following ocular surgery, trauma or in patients with ocular surface compromising state such as exposure keratopathy. In this study we aimed at assessing the conjunctival flora in ICU patients treated for the prevention of exposure keratopathy.

Methods: This is a post-hoc-analysis of data collected from a prospective, randomized-double-blinded study examining different treatments for the prevention of exposure keratopathy in ICU patients including punctal plugs, bandage contact lenses and lubrication-only control group. The first two groups were additionally treated by topical-antibiotics (ofloxacin or Chloramphenicol)

Results: One hundred and five patients were included in this study. Patient demographics and ICU baseline treatment were similar between groups. The three groups did not differ significantly in flora composition. Coagulase-negative-staphylococci (CoNS) were the most prevalent organisms among eye cultures (N=79, 75%). Right-eyes had more CoNS (P=0.0233). A positive correlation was found in CoNS culture between the eyes (rs=0.25,P=0.036). CoNS were more prevalent in positive conjunctival cultures than in positive blood cultures (Right-eye:74.68% vs 21.05%, P <0.001;Left-eye:56.14% vs 21.05%, P <0.001).. The groups treated with topical antibiotics had less gram-negative microbes in their cultures (P=0.025).

The degree-of-keratopathy at day-32 was correlated to CoNS positive blood-sample (Right-eye, rs=0.27, P= 0.013;Left-eye, rs=0.29, P= 0.007) (Right-eye, rs=0.27, P=0.014 ;Left-eye, rs=0.27, P=0.014).

Conclusion: As reported for normal patients, CoNS are the most prevalent microorganisms in the conjunctival flora, and are probably less affected by topical fluoroquinolones or Chloramphenicol than Gram-negative microbes. Since CoNS are the most common pathogens causing bacterial keratitis, possibly, different antibiotic regimens should be employed in ICU patients exhibiting frank exposure keratopathy or treated for the prevention thereof.

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Oncology
VOD

Vismodegib for POLA BCC: A Predictive Model For Tumor Response and A Novel Treatment Algorithm

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Purpose: To establish a model to predict treatment outcome of periocular locally advanced basal cell carcinoma (POLA BCC) based on initial response to treatment with vismodegib (ErivedgeTM), a sonic hedgehog inhibitor.

Design: Subgroup analysis of data from the STEVIE study database.

Methods: Analysis of medical history, treatment protocol, and treatment outcome of POLA BCC tumors in a STEVIE study population of 244 POLA BCC patients treated with ≥1 dose of vismodegib.

Results: A predictive model for complete response (CR) was established based on the initial treatment response. A cutoff value of 20% reduction in tumor size at 3 months of treatment identified the patients with a high probability (82.76%) to achieve CR. A second cutoff value of 67% reduction in tumor size at 6 months of treatment improved the prediction to a 95.42% probability of a CR outcome. Response to treatment was better for smaller tumors (≤10 mm) compared to 2 groups of larger tumors (>10 and ≤20 mm, >30 mm). The group with smaller tumors also had a significantly higher CR rate compared to the groups with larger tumors (P = 0.003 and P = 0.007, respectively). Progressive disease was present only in the group with the largest tumors (P = 0.002).

Conclusions: A treatment model was constructed based on the prediction of a CR outcome and the initial response to vismodegib treatment at 3 and 6 months. The resultant significant new insights can facilitate decision-making on treatment management according to tumor response in patients with POLA BCC.

Glaucoma
VOD

Surgical outcomes of Ahmed glaucoma valve implantation with plate fixation with Vicryl sutures or no plate fixation

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Purpose: To summarize the surgical outcomes of Ahmed glaucoma valve (AGV) implantation with plate fixation with Vicryl absorbable sutures or no plate suturing.

Methods: This study was a retrospective case series that included all glaucoma patients who underwent AGV implantation surgery with Vicryl absorbable sutures for plate fixation or without plate fixation, performed by a single surgeon between 2014-2019. We reviewed their medical records and retrieved clinical data on intra- and postoperative complications, best-corrected visual acuity, intraocular pressure (IOP) and number of IOP-lowering medications.

Results: Twenty of 29 eyes (29 patients, mean age 61.04 ± 27.1 years, 17 men) underwent AGV implantation without plate fixation and nine had AGV implantation with fixation with Vicryl sutures. Plate-related complications were observed in 15 cases (51.7%). Reoperation was required to remove the AGV in nine cases, and the original surgery was defined as failure, of which five were no-fixation cases (5/20, 25%) and four were Vicryl-fixation cases (4/9, 44.4%). Seven of all surgical failures were related to AGV migration (7/9, 77.7%). There were three cases of extrusion and one case of plate migration in the no-fixation group, and two cases of plate migration and one case of extrusion in the Vicryl-fixation group.

Conclusion: Either AGV implantation without suture plate fixation or AGV implantation with Vicryl fixation had a high complication and failure rate, often necessitating reoperation and AGV removal. The high rate of tube-related complications observed after both techniques does not favor either of them. The use of non-absorbable sutures for suturing of the AGV plate is recommended.

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Genetics
Live+VOD

Novel compound heterozygous RBP3 mutations cause high myopia

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Purpose: Identifying the molecular genetic basis of high myopia since infancy in a girl of Ashkenazi Jewish descent.

Methods: The affected individual underwent thorough ophthalmologic examination. Genomic DNA was extracted from whole blood samples of the affected individual and the unaffected parents. Linkage analysis (750K SNP; online Homozygosity-Mapper software analysis) and whole exome sequencing were done. Next generation sequencing (NGS) data were analyzed using our in-house tool, filtering through our in-house 582 controls and available databases, based on allele frequency, linkage locus, indel mutation analysis, etc. NGS results were verified through Sanger sequencing.

Results: The affected girl presented at age 15 months with high myopia (spherical equivalent -11.00 diopters in each eye) and fundus changes compatible with myopia. No nyctalopia or photophobia were noted. Linkage analysis yielded disease-associated loci on chromosomes 6 and 10. A single heterozygous missense mutation (c.3341G>A ; p.Arg1114Gln) in RBP3 was found within the chromosome 10 locus, analyzed using our in-house databases along with open access databases and verified through Sanger sequencing. In addition, CMA identified a ~5 million bp heterozygous deletion, encompassing RBP3, within that locus. Integrative Genomics Viewer (IGV) analysis of NGS data was used to confirm the deletion mutation, showing ~50% less reads in the deleted region compared to controls. Segregation analysis demonstrated that the missense mutation was inherited from the heterozygous father and that the deletion mutation was de-novo, not found in both parents.

Conclusions: The ocular phenotype of infantile high myopia was caused by a novel compound heterozygous mutations in RBP3 gene: an inherited heterozygous missense c.3341G>A mutation and a large de-novo deletion mutation encompassing RBP3, that was identified through Indel analysis and low levels of NGS reads of the patient compared to controls. This is a first report of large deletion mutation in RBP3, which we show to be an unusual "second hit" de-novo germline mutation. Genetic diagnosis is important in children presenting with infantile high myopia, which can be the presenting sign of a degenerative ocular disorder.

The Prevalence of Cystoid Macular Edema in Children with Retinitis Pigmentosa and Leber Congenital Amaurosis

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Purpose: Cystoid macular edema (CME) is a common complication in retinitis pigmentosa (RP) and Leber congenital amaurosis (LCA) patients, with a reported prevalence of 11-50% in adults. However, CME prevalence in the pediatric RP population has not been addressed. The aim of our study was to assess the prevalence of CME in pediatric RP/LCA patients detected by optical coherence tomography (OCT).

Methods: Medical records of children up to age 18 with a diagnosis of RP/LCA were reviewed retrospectively; only those who performed an OCT scan were included in the study. Diagnosis was based on history of poor vision since birth, nyctalopia, visual field constriction, characteristic fundus findings on clinical examination or electroretinogram (ERG), and/or genetic testing. OCT images were reviewed and assessed for macular cystic changes. Patients with more than one hyporeflective cystic macular space with well-defined boundaries were included.

Results: Of the 51 children (age 4-18 years, mean 10.8±4.0) diagnosed with RP, 16 had CME (31.3%) diagnosed by OCT, 14/16 (87.5%) had bilateral CME and 2 patients (12.5%) had unilateral CME. Among children with CME, 8 had an identified causative gene; among them 7/8 (87.5%) were inherited in an autosomal recessive fashion and 3/8 (37.5%) children had biallelic CRB1 mutations. CME was treated in 11/16 children and 4/11 had some improvement; 1/4 had improved vision (one line gain in vision for distance and near) and 3/4 had reduced central foveal thickness with stable vision.

Conclusions: Our results show that as many as one-third of children with RP/LCA will manifest cystic changes on OCT, comparable to the reported prevalence of CME in adults. Since clinical suspicion of cystic retinal lesions is challenging in children, it is necessary to screen these children by OCT to exclude the presence of CME. Early treatment of CME may potentially lead to better visual outcome. Additional long-term research is needed to assess recommended treatment and its efficacy on CME in pediatric RP/LCA patients.

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Genetics
Live+VOD

Complex ABCA4 alleles complicate Genetic Counseling in Stargardt disease

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Purpose: Most disease-causing alleles contain a single pathogenic mutation in the causative gene. Complex alleles are characterized by at least two variants that are located on the same allele. In some cases, each variant will partially contribute to pathogenicity, thereby resulting either in pathogenicity of the complex allele or in a more severe phenotype. While complex alleles are considered rare, a large number have been reported in ABCA4, the major cause of Stargardt disease. In addition, over a dozen hypomorphic variants have been reported in ABCA4. The purpose of the current study is to examine whether p.G1961E, the most common ABCA4 mutation in the Israeli population, exists as a complex allele.

Methods: Sequencing was either performed using the Sanger method or by sequencing the entire ABCA4 locus by smMIPs analysis. Ocular evaluation included a full ophthalmological examination.

Results: We identified 51 index cases who harbored p.G1961E either homozygously (17 families) or in compound (or suspected compound) heterozygous state with another ABCA4 pathogenic variant (36 families). While 7/17 homozygous index cases did not carry other ABCA4 mutations, interestingly most (10/17- 59%) carried complex alleles, the majority of which (8 heterozygously and 1 homozygously) included the missense variant p.R1640Q that has been found only in patients of Yemenite Jewish origin and is a relatively common founder mutation in this population. On the other hand, only 11/36 (31%) compound heterozygous index cases carried a complex allele, 5 of which that were of Ashkenazi Jewish origin included the deep intronic variant c.769-784C>T. On average, patients who are homozygous for p.G1961E only, had better visual acuity (0.42) compared to patients who also carried p.R1640Q (0.21).

Conclusions: The frequency of the ABCA4-p.G1961E variant in the Israeli population is relatively high and therefore 5000 individuals in Israel are expected to be homozygous and therefore might suffer from Stargardt disease if fully penetrant. Our data suggest that in most cases p.G1961E is part of a complex allele increasing its penetrance, while other p.G1961E alleles might not be pathogenic. Our findings indicate that one needs to be cautious when determining the pathogenicity of ABCA4 variants, and especially those related

to p.G1961E, and that genetic counseling for ABCA4 might be challenging and require more attention than for other causative genes.

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Oculoplastics
VOD

The Effect of Chalazion Surgery on Dry Eye Syndrome and Meibography

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Objectives: To evaluate the effect of incision & curettage (I&C) surgery for chalazion excision on dry eye syndrome by meibography and subjective measurements a s well.

Methods: This prospective, interventional clinical study, included adult patients with a primary chalazion which persisted despite conservative treatment. All patients underwent I&C surgery. The following parameters were compared both preoperatively and 21 days postoperatively: Meibography, tear breakup time (TBUT), Schirmer test, meibum expression, tear meniscus height, meibomian gland dysfunction (MGD) grading, and the Ocular Surface Disease Index (OSDI).

Results: Thirty eyelids of twenty four patients were enrolled in the study. The mean age ± SD was 40.56±13.94 years. There was a significant change in MGD grading postoperatively. A significant decrease in meibomian gland loss and meibum expression score were noted (P=0.00 and P=0.00, respectively). The most common meibomian gland morphology noted preoperatively included fluffy areas and tortuous glands, and both improved postoperatively (P=0.04 and P=0.02, respectively). There was no significant difference in Schirmer test score. TBUT and tear meniscus height also improved significantly (P=0.00 and P=0.003, respectively). The OSDI score improved significantly too, (P=0.00).

Conclusions: According to our study, I&C surgery lead to an improvement of the subjective feeling of dry eye as well as objective dry eye parameters, including meibomian gland morphological characteristics, meibomian gland loss, MGD grading, and TBUT. Therefore, it appears to be beneficial to operate on chalazion patients earlier after conservative treatment failure in order to improve their dry eye syndrome.

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Anterior segment
Live+VOD

Capturing limbal epithelial stem cell population dynamics, signature & niche

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Purpose: To discover new limbal stem cell (LSC) populations, their genetic signature, cycling properties and niche.

Methods: We performed single-cell RNA sequencing, cell populations were identified in silico and validated by in situ hybridization and immunofluorescent staining. Quantitative lineage tracing was performed to follow clonal growth and pattern over time, proliferation analysis was by nucleotide incorporation assays and niche immune cell function were explored using immunodeficient mouse models and topical immune repressors.

Results: We report the identification of previously undescribed LSC populations that reside in separate and well-defined sub-compartments. In the “outer” limbus, we discovered a primitive widespread population of quiescent LSCs (qLSCs) that uniformly express Krt15/Gpha2/Ifitm3/Cd63 proteins that serve as SC reservoir and in boundary formation. In the “inner” peri-corneal limbus, we identified prevalent active LSCs (aLSCs) that express Krt15-GFP/Atf3/Mt1-2/Socs3 and maintain homeostasis. We propose that these SC populations are abundant, follow stochastic rules and neutral drift dynamics. Notably, we provide evidence that T cells serve as niche cells for qLSCs, regulating quiescence and wound response.

Conclusion: This study provides a useful atlas that uncovers the main corneal epithelial cell populations, capturing the signature and the niche of quiescent and activated LSC states. These data open new research avenues for studying the mechanisms of cell proliferation and differentiation as well as the applications of LSCs in regenerative medicine.

Prediction of age-related macular degeneration (AMD) in the Israeli population based on polygenic risk scores (PRS): preliminary results

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Purpose: A recent AMD genome-wide association study has identified 52 independently associated common and rare genetic risk variants. These findings facilitate the prediction of the genetic predisposition to the disease. The main objective of this project is to evaluate the performance of polygenic risk scores for AMD in the Israeli population.

Methods: We used the International AMD Genomics Consortium (IAMDGC) summary statistics to generate polygenic risk scores (PRS) for Israeli AMD patients and controls (n = 659, AMD/controls: 403/256). We applied pruning of correlated variants (prioritizing strongly associated variants) and thresholding by P-value. We evaluated the accuracy of PRSs by the under the receiver operating characteristics curve (AUC).

Results: The proportion of AMD patients is consistently higher in top quantiles of the PRS. The AUC was moderately higher in a model that included the PRS, age, sex, and ancestry (principal components), compared to a covariates-only model (0.77 [95% CI:0.73-0.8] and 0.73 [95% CI:0.7-0.77], respectively). Addition of genetic variants with p-values beyond the genome-wide significance threshold (5 × 10^(−8)) did not improve the performance of the model.

Conclusions: Our preliminary results show that the contribution of PRS to the predictive ability of the model is evident but modest. In future work, we will optimize the PRS development process, which may improve its discriminatory power.

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Visual function
Live+VOD

Machine learning Prediction of Alzheimer's Disease Using Chromatic Pupilloperimetry.

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Purpose: A family history of Alzheimer disease (AD) is a major risk factor for AD. The aim of this study was to identify early changes in the pupil light reflex (PLR) in subjects at high risk to develop the disease.

Methods: 186 subjects were enrolled, 125 offspring of AD patients (FH+) and 61 age-matched controls (FH-), ages 44-71. Ophthalmic assessments included a Chromatic Pupilloperimetry test and a complete ophthalmologic examination to exclude ocular pathologies. Cognitive assessment, to verify subjects were asymptomatic, included executive function and episodic memory tests. 35 pupilloperimetry features were measured in 54 spots in a 24-2 visual field. Machine learning classification models were trained such that each model was introduced to a single feature type (measured in 54 spots) in the training data, and the same hyperparameters and training protocol were used in all models. Each model was then tested to quantify how well it can discriminate between FH+/FH-. The accuracy of a model was used as an indication to the correlation of a feature type to AD family history, using a standard confidence interval (CI) of 95%.

Results: Chromatic pupilloperimetry based learning models were able to predict the existence or non-existence of AD family history with performance of ROC AUC of 0.89 ± 0.03, 95% CI of [0.81, 0.93] (left eye) and 0.86 ± 0.03, 95% CI of [0.81, 0.91] (right eye). Chromatic pupilloperimetry parameters associated with the contraction arm of the PLR were more discriminative then parameters associated with the relaxation limb..

Conclusions: Our results show that AD family history status could be predicted with high discriminative values using chromatic pupilloperimetry PLR parameters. This could imply that subtle changes in pupil contraction, associated with AD could be detected years before the onset of the disease using a simple non-invasive test.

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Pediatrics
VOD

Adherence to anti amblyopia therapy during the first COVID-19 closure

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Purpose: To study the change in compliance to anti-amblyopic treatment during the COVID-19 pandemic in children who are treated at home and in school with glasses and/or patching.

Methods: Patients aged 6 months to 7 years who are under treatment for amblyopia were recruited in the pediatric ophthalmology clinic in Hadassah, and through electronic medical records. The patient's parents were interviewed over the phone or in the clinic. The following information was gathered on all patients: age, visual acuity in each eye, prescribed treatment regimen, duration of treatment, routine treatment site, and reported compliance to treatment before and during the COVID-19 closure.

Results: Forty eight patients, aged 6 months to 7 years (44m±15.76), were included in the study. Patients were prescribed glasses (28, 58.33%), 1-2 hours of patching (37, 77.1%) or 3-6 hours of patching (7 ,14.6%). Patients were treated mostly at home (21, 44%) or mostly in school (21, 44%), with only three children treated equally at home and in school. Overall compliance before the COVID-19 pandemic was good in 39 children (81.2%), and limited in 9 (18.8%). Overall compliance decreased during the first closure (03/14/20-05/14/20) in 18 patients (37.5%). Compliance decreased in more patients who were treated in school before the closure (13/21, 61.9%), than those treated at home (5/21, 23.8%, p=0.013). A non statistically significant trend towards better compliance during the lockdown was seen in patients who were prescribed less hours of patching. The compliance of patients who were using glasses was similar to that of those using patching. Other variables (age, number of children in the family, duration of treatment and visual acuity) did not have an effect on the change in compliance during the closure.

Conclusions: Patients who are usually treated at home adapted better to the change in their daily routine during the COVID-19 closure, suggesting that maintaining a routine of treatment at home and probably in school too, improves the compliance to anti-amblyopic therapy. Such a routine may be especially important among patients with more daily patching hours, who are prone to lower compliance to treatment.

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Visual function
VOD

Validation of a novel test for detection of astigmatism

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Introduction: Visual search describes the detection of an odd element within a field of distractors. Astigmatism affects visual perception by blurring the retinal image of a spot along a particular orientation rendering an elliptical shape. The Wilkins Egg and Ball Test was created based on these principles. The test consists of three pages, each comprising 10 rows in which patients are asked to identify the one circle hidden within a row comprising nine ovals. Patients with astigmatism are hypothesized to encounter difficulty in differentiating between oval and circular targets compared to normal patients. This study examined the utility of the test in identifying patients requiring astigmatic correction.

Methods: Non-astigmatic participants (N=37, mean age: 26± 5, range: 16-26, 11 male) and participants with astigmatism (N=28, mean age: 36± 10, range: 18-36, 9 male) with mean cylindrical corrections of 2.80 ± 0.70 DC (range: -2.00 DC to -4.00 DC), were recruited. Participants were asked to detect the circle in each of the ten rows of each page, while the experimenter recorded their search time (sT) and number of errors(noE). Non -stigmatic participants were examined under five conditions (baseline, and induced cylinder at four primary meridians) and participants with astigmatism were examined under corrected and uncorrected conditions, in random order. The sT and noE of varying conditions were compared using the Friedman test.

Results: In non-astigmatic participants, sT was significantly quicker and the noE was significantly lower in the baseline condition (38±9 sec, 0.97±1.5 errors) compared with all induced cylinder conditions (approximately 54±19 sec, 2.35±2.2 errors $p<0.05$ for all except for the induced 90 deg astigmatism condition,). In participants with astigmatism, the corrected condition was 6 sec faster with one less error on average, though these differences were non-significant.

Conclusion: The potential of the Wilkins Egg and Ball test for detection of uncorrected astigmatism remains uncertain . Results of the induced astigmatism are promising, though findings from the astigmatic sample were non-significant. More participants are being recruited to draw definitive conclusions.

In-vivo imaging for assessing tumor growth in a mouse models of choroidal melanoma

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Purpose: Choroidal melanoma (CM) is an ocular malignancy that gives rise to life-threatening metastases. Although local disease can be treated successfully, it is often at the cost of significant impairment of vision and treatments are not effective against metastatic disease. Novel treatment modalities which preserve vision may enable elimination of small tumors and may prevent subsequent metastatic spread. Very few mouse models of metastatic CM are available for research and for development of novel therapies. One of the challenges is to follow tumor growth in-vivo and to determine the right size for treatment. Hence, the purpose of this study was to establish a simple, noninvasive imaging tool that will simplify visualization and tumor follow-up in a mouse model of choroidal melanoma.

Methods: Tumors were induced by inoculation of murine B16LS9 cells into the choroidal space of a C57BL/6 mouse eye. Five to ten days following injection, tumor size was assessed by Phoenix MicronIVTM image-guided Optical Coherence Tomography (OCT) imaging, which included a real-time camera view and OCT scan of the retina, and by histopathological examination of eye sections.

Results: Tumor growth was observed 5-9 days following sub-retinal injection of B16LS9 cells. A clear tumor mass was detected in the choroid using the MicronIVTM imaging system camera and OCT scans. Histology of eye sections confirmed the presence of tumor tissue. OCT allowed an accurate measurement of choroidal tumor size. Moreover, OCT enabled assessing the success rate of the choroidal tumor induction by confirming the presence of local or broad retinal detachment (RD) following tumor cells injection, or leakage of the cells into the vitreous. Importantly, we found a correlation between RD height on the day of cells inoculation and tumor size on day 5. Hence, it is possible to predict tumor size at later stage already on the day of cells injection.

Conclusion: We have established a reproducible model for evaluating choroidal tumor size in-vivo, without sacrificing the animal. By using a simple, non-invasive imaging tool, we were able to accurately measure tumor size, assess the success rate of the choroidal tumor induction, and to define, already at the time of cell inoculation, a grading scale for predicting final tumor size. This tool may be utilized for evaluation of new mouse models for choroidal melanoma, as well as for testing new therapies for this disease.

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Genetics
Live+VOD

A novel LRRC32mutation in syndromic familial exudative retinopathy

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Purpose: To describe three cases with new gene mutation causing syndromic Familial Exudative Retinopathy.

Methods: Retrospective review of patientג€™s electronic medical records who were diagnosed with a new mutation in the LRRC32 gene.

Results: Three cases with retinal involvement and systemic manifestation were identified. One child presented with bilateral chronic retinal detachments. An unrelated infant had unilateral retinal detachment and ischemic retinopathy with temporal traction in the good eye, and her brother had peripheral ischemia with proliferative retinopathy in both eyes at birth, and was treated with prompt intravitreal Avastin injection to both eyes and one month later underwent retinal laser photocoagulation treatment in both eyes without the need for further procedures during 4 years of follow up.

All patients had systemic manifestations including cleft palate and developmental delay. One patient had an abnormal vermis and deletion of corpus callosum and the siblings had enlargement of brain ventricles. All 3 cases had the same mutation in the LRRC32 gene, encoding a TGF ²- receptor.

Conclusions: Very early diagnosis and treatment are crucial to halt the progression of the disease and may prevent an unfavorable visual outcome. Genetic testing confirmed a new mutation in the LRRC32 gene, responsible for the clinical features of FEVR in all infants.

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Genetics
Live+VOD

Utilizing Site-Directed ADAR RNA Editing as a Potential Therapy for Inherited Retinal Diseases

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Purpose: The adenosine deaminase acting on RNA (ADAR) enzyme modifies RNA by editing adenosines to inosines and can be utilized for correcting mutated RNA. Current gene therapies for inherited retinal diseases (IRDs) are limited by gene size, multiple encoded transcripts, and immunogenicity. Harnessing ADAR for editing might overcome these limitations and transience of the RNA targets makes it easy to fine tune. Many IRD-causing mutations can potentially be targeted for ADAR editing. Our aim is to identify such mutations that are common in the Israeli population and develop a reporter system for testing the editing efficiency of the gRNAs to ultimately use them in a therapeutic capacity.

Methods: We categorized IRD mutations identified in Israeli patients based on variant type and effect on the codon. The mutations were ranked into 3 groups: #1â€“missense to missense, #2- nonsense to missense, and #3- missense/nonsense to the WT sequence. The efficiency of ADAR correction was studied in HeLa cell lines over-expressing ADAR1/2. The reporting system includes plasmids containing mCherry and EGFP and gene fragments with the target mutations.

Results: We identified 534 Israeli mutations, 183 of which (34%) belong to Groups #2/3 and can potentially be edited by ADAR. 17% of these variants, if edited, will be recognized as their original sequences while 17% of variants, if edited, will be converted from a nonsense mutation to missense. We selected 3 nonsense mutations for further analysis: TRPM1-c.880A>T, FAM161A-c.1567C>T, and KIZ-c.226C>T. We then used RT-PCR followed by Sanger sequencing to measure the level of hADAR correction of a house-keeping gene reaching editing levels of up to 60%. We subsequently designed a reported plasmid to test the correction of nonsense mutations by inserting a gene cassette, with or without the studied mutation, in between the two reporters- mCherry and EGFP. This will allow a rapid and accurate analysis of the correction efficiency. These experiments are being performed and the results will be presented in the upcoming meeting.

Conclusions: The compiled list of the most common Israeli IRD variants is valuable for choosing candidates for both RNA and DNA editing therapies in the future. Employing gRNAs that can recruit ADAR to edit specific mutations without having to consider gene size, number of transcripts, or immunogenicity, has immense value in the quest to create safe and effective therapies for IRDs.

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Cataract
VOD

Risk factors for a phacodonesis surprise during cataract surgery in patients with Pseudoexfoliation

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Purpose: To evaluate the association of different preoperative parameters with surprise phacodonesis during cataract surgery among patients with pseudoexfoliation (PXF).

Setting

Wolfson Medical Center, Israel

Design A retrospective cohort study

Methods: We reviewed the charts of all PXF patients who underwent cataract surgery between the years 2013 to 2018. Preoperative parameters (demographics, biometry, intraocular pressure (IOP), endothelial cell count, pupil size, cataract density, glaucoma status, cup to disc ratio, number of glaucoma medications, prior intra-vitreous injections, risk for intraoperative floppy iris syndrome) were compared between patients with and without surprise phacodonesis. Binary logistic regression was used to calculate the predictive value of each parameter.

Results: Out of 396 surgical cases with computerized preoperative assessment during the time period, we included 127 eyes of 120 PXF patients without evidence of phacodonesis preoperatively. Mean age was 77.8±12.0 years, 63 (52.7%) were male and 106 (84.2%) underwent phacoemulsification surgery. We identified 10 cases of surprise phacodonesis during surgery (8.2%). Compared to PXF cases without intraoperative phacodonesis they had higher preoperative IOP (23.0±11.0 mmHg vs 14.9±3.8 mmHg, p<0.001) and higher rate of B scan use due to dense cataract obscuring posterior pole evaluation [4 (40%)vs 15 (12.8%), p=0.04]. Multivariant binary logistic regression confirmed that only baseline IOP contributed to prediction of surprise phacodonesis (OR 1.22 CI:1.04-1.43, p=0.014).

Conclusions: Among patients with PXF undergoing cataract surgery elevated IOP and poor posterior segment visibility requiring B scan use were associated with zonular instability putting these patients at risk for intra-operative complications.

Chromatic pupilloperimetry for diagnosis and monitoring of patients with brain tumors without contact with the visual or pupil light reflex systems

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Purpose: To characterize the pupil light responses (PLR) for small focal chromatic light stimuli presented in peripheral and central retinal locations in patients with a mass effect due to brain tumors with no apparent contact with the visual or PLR systems.

Methods: The PLR for small (0.43°) blue and red-light stimuli presented at peripheral (21°) and central (4.2°) visual field (VF) locations were measured using chromatic pupilloperimetry in 6 patients with brain tumors with no apparent contact with the visual or PLR systems and 32 age-similar controls. All subjects underwent a complete ophthalmic exam, standard Humphrey automated perimetry (24-2), color vision test, best-corrected visual acuity, refraction and Spectral-Domain Optical Coherence Tomography (SD-OCT) imaging. All patients underwent brain MRI before and following tumor removal surgery.

Results: The SD-OCT thicknesses of macular ganglion cell and inner plexiform layers, as well as peripapillary retinal nerve fiber layer, were within normal limits in all patients. Differences in cone-mediated PLR were statistically insignificant between patients and controls. By contrast, rod-mediated percentage of maximal pupil contraction was significantly lower in patients compared to controls in the center of the VF (mean ± SD: 11% ±4 % vs. 16 %±5 %, p= 0.028, ROC AUC=86.6%, p=0.005). Melanopsin-mediated PLR was attenuated in the peripheral VF (p=0.005, ROC AUC=95.3% p=0.001). The rod- but not the melanopsin-mediated PLR recovered by 4 weeks post-OP.

Conclusions: Chromatic pupilloperimetry may present a fast, objective non-invasive test for diagnosis and monitoring of patients with brain tumors with no apparent contact with the visual or PLR systems. Short and long term mass effects on PLR pathways can be identified by multiparametric analysis of the PLR for focal chromatic stimuli at central and peripheral VF. Localized melanopsin-mediated sustained PLR may provide a novel surrogate biomarker for mass effects.

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Neuro-ophthalmology
VOD

Ophthalmological manifestations of vertebrobasilar stroke

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Purpose: Ophthalmological symptoms and signs of vertebrobasilar stroke (VBS) are not well described. In this study we summarized a large series of patients with ophthalmological manifestations following VBS.

Methods: Files of patients diagnosed and treated at a medium size hospital between 2015 and 2019 were collected. Clinical data from the medical files was reviewed. Data included demographics, risk factors, neuroimaging, ophthalmological symptoms and signs, visual field test and visual outcome.

Results: 19 patients were included, 57% underwent an eye exam at presentation. Mean age was 6713 ±, years, 84% were male. Risk factors for micro- vascular disease were diabetes mellitus (21%), hyperlipidemia (42%) and hypertension (36%). Ophthalmological manifestations were detected in 89% of patients, including visual field defect (31%) and anisocoria (15%). In addition, eye movement disorders such as new onset strabismus (15%), ptosis (11%) and nystagmus (21%) were documented. Brain stem stroke syndromes (10%) including Millard-Gubler Syndrome (5%), and Nothangel (5%) were diagnosed

Conclusion: The majority of patients with VBS had ophthalmological manifestations, but only 57% of them had an eye exam at presentation. Visual complaints are uncommon. There is a significant impact of detecting visual impairment on rehabilitation. We recommend a multidisciplinary team approach to vertebrobasilar stroke management.

Chromatic pupilloperimetry for objective visual field testing in Glaucoma patients

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Purpose: To objectively assess visual field defects in glaucoma patients using chromatic pupilloperimetry.

Methods: Eighteen glaucoma patients (10 females and 8 males, age: 70.9±7.4, mean± SD) and thirty healthy age-matched controls were enrolled (16 females and 14 males age: 67.2±5.5 mean). The pupil light responses (PLR) for focal blue and red light stimuli (peak 485 and 624 nm, respectively) presented at 54 targets (0.43°) in a 24-2 visual field were recorded and were correlated with patients' Humphrey 24-2 perimetry.

Results: Significantly lower percentage of pupil contraction (PPC) was recorded in scotomatous areas in the glaucoma patients in response to dim blue light stimuli. A milder defect was recorded in response to red light stimuli. Glaucoma patients demonstrated attenuated melanopsin-mediated PLR at the center and nasal VF (p=.000137 and p=.009, respectively).

Conclusions: Chromatic pupilloperimetry may enable objectively assessment of VF defects in glaucoma patients. Multiparametric analysis of the PLR identifies defects in intrinsic and extrinsic activation of intrinsically photosensitive retinal ganglion cells in glaucoma.

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General
VOD

Ocular involvement in coronavirus disease 2019 (COVID-19): a clinical and molecular analysis

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Purpose: Coronavirus disease 2019 (COVID-19) caused a global pandemic with millions infected worldwide. Little is known on the ocular involvement associated with the disease. The aim of this study was to to assess the clinical and molecular ocular involvement among patients with confirmed COVID-19 admitted to a tertiary care facility.

Methods: Consecutive patients admitted to the COVID-19 Ward of the Shamir Medical Center in Israel during March and April, 2020 were included. The control group included patients negative for COVID-19 admitted during a similar period to a different ward. Patients were examined by trained Ophthalmologists. SARS-CoV-2 conjunctival swab samples were obtained.

Results: Included were 48 patients, 16 with confirmed COVID-19 and 32 controls. Median patient age was 68.5 (interquartile range: 31.5, mean: 63±21) years and 48% were male. Active conjunctival injection was present in three patients (19%) with COVID-19, compared to none in the controls (p=0.034). Patients with COVID-19 were more likely to complain of foreign body sensation (31.3% vs. 3.1%, p=0.005) and redness of the eye (25% vs. 0%, p=0.003). Conjunctival injection was associated with loss of smell and taste (75% vs 7.7%, p=0.018). Viral conjunctival swab tests all showed negative results for all three viral genes tested (E, N, and RdRp).

Conclusions: Among patients admitted to a tertiary referral center with confirmed COVID-19, active conjunctival injection was noted in one out of five cases, and was associated with loss of smell and taste. Conjunctival swabs for viral RNA were negative in patients with and wi thout ocular involvement.

Housing RCS rats under SPF conditions alters intestine microbiota and ameliorates retinal degeneration

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Purpose: To investigate the association between gut microbiome composition and retinal degeneration rate in RCS rats raised in specific pathogen free (SPF) and non-SPF conditions.

Methods: RCS rats were born and raised in Sheba Medical Center animal facility under SPF (n=69) and non-SPF conditions (n=48). Fecal samples were individually collected every two weeks for microbiome analysis and the rats were examined for retinal structure by Spectral Domain Optical Coherence Tomography (SD-OCT), blue light autofluorescence fundus (BL-FAF) imaging and histopathology. Retinal function was assessed by Electroretinogram.

Results: Gut microbiome significantly differed between rats that were raised in non-SPF vs. SPF conditions. 90 different bacterial amplicon sequence variant (ASVs) were increased in non-SPF and other 34 bacterial ASVs were increased in SPF raised rats. Specific bacterial ASVs showed increased abundance with increasing rat age, and those were observed in earlier ages in rats raised in non-SPF conditions compared to rats raised in SPF conditions ($p=0.002$). BL-FAF imaging revealed significantly smaller hypofluorescent lesions in rats raised in SPF conditions. This was more specifically noted at the age of 12 weeks, where the hypofluorescent lesion area was 6.8 fold higher non-SPF rats vs. rats raised in SPF conditions ($p=0.003$). Significantly shorter latencies were recorded for scotopic a- and b-waves and photopic b-waves in rats raised in SPF conditions as early as 4 weeks of age compared to rats raised in non-SPF conditions ($p=0.02$, $p<0.001$, $p<0.001$ respectively). At age of 8 weeks, the scotopic a-wave latency recorded in rats raised in non-SPF conditions was 1.7 fold longer (57.69 ± 11.57 ms) compared to rats raised in SPF conditions (33.11 ± 2.93 ms, $p=0.04$). SD-OCT total retinal thickness was higher in the superior part of the retina in rats raised in SPF conditions (294.83 ± 12.64 um) compared with rats raised in non-SPF conditions (260.327 ± 10.76 um, $p=0.05$).

Conclusions: Microbial diversity and age-related microbial dynamics were observed in non-SPF vs. SPF rats, in parallel to more rapid and severe retinal degeneration, and may present potential intervention strategy for slowing disease progression.

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Retina
VOD

Gut-retina axis in Retinitis Pigmentosa (RP): Antibiotic treatment has a protective effect on retinal degeneration in two RP rodent models

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Purpose: Evaluation of gut microbial composition and changes in retinal structure and function following antibiotic treatment in rodent models of retinitis pigmantosa.

Methods: RCS rats and RPE65/rd12 mice were born and raised at the Sheba Medical Center SPF animal facility. Dams were given a cocktail of antibiotics (ampicillin, neomycin, metronidazole, and vancomycin) dissolved in the drinking water to remove indigenous gut microorganisms. Antibiotic treatment continued from pregnancy of the dams to age of 12 weeks of the pups. Fecal samples were individually collected every two weeks for microbiome analysis and the animals were examined for retinal structure by Spectral Domain Optical Coherence Tomography (SD-OCT), blue autofluorescence fundus imaging (BL-FAF) and histopathology. Retinal function was assessed by Electroretinogram (ERG).

Results: RCS rats (n=16) treated with antibiotic presented with higher a- and b-wave maximal ERG responses compared with non-treated rats (n=31) at the ages of 4-6 weeks ($p<0.001$). Significantly higher a- and b-wave maximal ERG responses were recorded in mice treated with antibiotics (n=8) at the age of 8 weeks compared to untreated mice (n=11) at the same age ($p<0.001$).

Conclusion: Antibiotic treatment delays retinal degeneration in rodent models of RP in early ages. These results shed light on the gut-retina axis and may suggest a novel therapeutic approach for RP.

Novel flavonoid-based eye drops for treatment of retinal degeneration

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Purpose: To assess the safety and efficacy of a novel flavonoid (TTF)- based eye drops formulation for treatment of retinal degeneration.

Methods: Eye cups of 21 day-old RPE65/rd12 mice were incubated in media supplemented with 8nM TTF or the same volume of vehicle solution for 18 hours. Sections were stained with antibodies directed against cone opsins and counter-stained with DAPI. The number of positively stained cells/mm retina was recorded. Rabbits were treated with TTF eye drops and TTF concentration in anterior chamber tap removed at 5, 45, and 180 minutes was determined by HPLC to determine corneal permeability. RPE65/rd12 mice were treated twice daily, 6 days/week, for 12 weeks with eye drops containing either TTF (12.5mg/ml, n=16) or vehicle (n=16). RPE /retina flat mounts were stained with Iba-I to assess microglial activation and retinal sections were stained with TUNEL to assess treatment effect on photoreceptor apoptosis. Retinal function was determined by electroretinogram (ERG).

Results: Supplementation of 8nM TTF rescued cones photoreceptors from degeneration in the eye cups cultures in vitro. TTF penetrated the corneal barrier in rabbit eyes. The maximal concentration of TTF in anterior chamber taps was 1.7 μM, 45 minutes following eye drops instillation. Three-week treatment with TTF eye drops significantly reduced microglial activation and migration into the sub retina compared to vehicle (mean ± SD: 42±14 microglia cells/retina vs. 143 ± 28 microglia cells/retina, p=0.0063). The number of TUNEL positive cells in the photoreceptor layer was significantly lower in treated mice compared with control (mean ± SE: 2 ± 0.4 apoptotic cells/mm retina vs. 6 ± 0.8 apoptotic cells/mm, p=0.0013). A significantly higher scotopic ERG a-wave was recorded in treated mice 3 weeks following treatment initiation (p=0.005).

Conclusion: TTF eye drops may present a novel simple treatment for retinal degeneration, reducing microglial activation and inflammation, preventing photoreceptor cell death, and preserving retinal function in a mouse model of RP. No side effects were observed following 12 weeks of daily treatment with the TTF eye drops, supporting the potential feasibility for clinical application as a treatment for incurable blinding diseases.

85
Cornea
VOD

Pterygium Excision Peeling Without a Knife

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Purpose: A pterygium is fleshy tissue that grows in a triangular shape onto the cornea. Indications for surgery include visual impairment, cosmetic disfigurement, motility restriction, recurrent inflammation, interference with contact lens wear and rarely, changes suggestive of neoplasia. Until now many surgical techniques have been used, though none is universally accepted. A sharp cutting tool is used to create a cleavage and dissected firm adhesion of the pterygium from the cornea and then dissecting the remaining head from the corneal surface. The body of the pterygium bleads and blocks the surgical field of view. This study aims to introduce a new easy and fast method which may aid to remove the pterygium head without the use of sharp cutting tools.

Methods: Lidocaine (2%) was injected under the body of the pterygium. The pterygium removal process included resection of the pterygium head and tenonג€™s capsule by two surgical sponges (triangular, e.g. Weck-cel). One was inserted under the body of the pterygium at the limbus and the second was used to push and pull the head with toothed forceps. Tenonג€™s capsule was removed, and the head and the body of the pterygium were excised. A conjunctival autograft devoid of Tenonג€™s capsule was prepared from the superotemporal conjunctiva.

Results: The surgical sponges induced push pull forces and dryness of the pterygium head resulting in fast (within less than a minute) peeling of the pterygium from the cornea without the need of cleavage. The sponges also better absorb local bleeding allowing better visualization of the surgical field.

Conclusion: Pterygium removal was successfully obtained using readily accessible surgical sponges, without extra scraping and substantially less bleeding during this procedure. This procedure may minimize post-operative complications that include ocular perforation, as well as possible retinal detachment or endophthalmitis that might occur as a result of inadvertent perforation of the globe.

Three decades of retinoblastoma in Africa: 1989-2019

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Purpose: It is estimated that more than 25% of global retinoblastoma (RB) cases, the most common ocular malignancy, occur in Africa. Little is known, however, about the clinical features of RB in African countries. We aimed to conduct a systematic review of the current evidence, focusing on the stage at presentation and outcome of RB in Africa in the last three decades.

Methods: PubMed and EMBASE were searched using the terms retinoblastoma and Africa or the names of African countries using a custom Python script. We retrieved publications from January 1989 to July 2019. Papers containing information about clinical features or epidemiological data, and for which data collection started after January 1st, 1989, were eligible for inclusion. A single estimate of survival for each country was calculated. Data on economic grouping were retrieved from the World Bank.

Results: Of the 727 records retrieved, 67 studies met the eligibility criteria, with a total sample of 5,899 patients. Of these, 55% were males and 45% were females. Average age at time of diagnosis was 35.5±7.2 months for unilateral disease and 20.9±0.9 months for bilateral disease. The mean delay from first symptoms to treatment was 9.6±1.2 months. Clinical features at diagnosis included leukocoria in 54% of cases, proptosis in 24% and strabismus in 9% of cases. While in low-income countries (LICs), leukocoria was evident in 47% and proptosis in 27% of cases, in lower-middle income countries (LMICs), leukocoria was the presenting sign in 65% and proptosis in 17% of cases ($p<0.001$). Of the sample, 36% of cases had extra-ocular disease at time of diagnosis. This percentage varied between countries with different economic status, with 43% of cases in LICs compared to 21% in LMICs. Overall survival in 15 African countries for which the data were available was 60%. When calculating survival per decade, the estimated survival was 20%, 58% and 75% for studies conducted during 1990-99, 2000-09 and 2010-19, respectively, with a statistically significant linear trend ($p < 0.001$). On sub-analysis according to economic grouping, estimated survival in LICs was 51% as compared to 76% in LMICs.

Conclusions: According to the present systematic review, clinical data on retinoblastoma in Africa is lacking, with only 67 publications found in the literature in the last three decades. Many children present with advanced disease and for many the outcome is dismal. However, survival rate has improved with time.

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Retina
Live+VOD

Protease Activated Receptor 1 (PAR1) is expressed in rods outer segments and nuclei of neuroretina cell

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Purpose: Protease-activated receptor-1 (PAR1) is activated by the action of serine protease Thrombin. Thrombin plays a role in neurological dysfunction in diabetes. Recent studies have indicated that PAR1 and its activating protease thrombin are expressed in the ocular microenvironment of patients with diabetic retinopathy (DR). The aim of this study is to characterize the distribution of PAR1 in the neuroretina, under physiological conditions and in diabetes.

Methods: Diabetes was induced in 8 weeks old C57BL/6J male mice by intraperitoneal injection of Streptozotocin (STZ, 150 mg/kg). Five weeks following diabetes induction eyes were removed from diabetic mice (n=12) and healthy C57BL/6J male mice (n=12) and were processed for indirect immunofluorescence analysis. PAR1-/- mice were used as control (n=3). In addition, western blot analysis was performed on mouse neuroretina, optic nerve, brain and platelets samples.

Results: A significant PAR1 staining was observed in the nuclei of all neuroretinal cell layers (retinal ganglion cells, inner and outer nuclear layers) in diabetic mice (glucose blood > 200mg/dl). Significantly weaker staining was observed in control non-diabetic mice. No staining was observed in PAR1-/- mice. Co-staining of PAR1 with photoreceptor markers demonstrated co-localization of PAR1 and rhodopsin in rod outer and inner segments. By contrast, no PAR1 staining was observed in cone outer segments. The specificity of immunofluorescence staining was confirmed by Western blot analysis.

Conclusion: To the best of our knowledge, this is the first demonstration of PAR1 expression in rod retinal photoreceptors and inner nuclear layer cells. This study suggests that PAR1/thrombin pathway may play a role in pathophysiology of rods in diabetic retinopathy.

Mapping intrinsically photosensitive retinal ganglionic cell dysfunction in patients with Parkinson disease using chromatic pupilloperimetry

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Purpose: To characterize the focal intrinsic and extrinsic light responses in intrinsically photosensitive retinal ganglion cells (ipRGCs) at central and peripheral retina in patients with Parkinson disease (PD).

Methods: Seventeen PD patients (mean age ± standard deviation: 61.29 ± 11.54 years) and 26 age-similar healthy controls (65.07 ± 11.22 years, p=0.29) were enrolled. The pupillary responses (PLR) for small (0.43 degrees) red and blue light stimuli presented at central (4.2 degrees) and peripheral (21 degrees) visual field locations were measured using a chromatic pupilloperimeter under mesopic light adaptation conditions. All subjects underwent a complete neurological evaluation along with the MDS-Unified Parkinson's Disease Rating Scale (MDS-UPDRS), Montreal Cognitive Assessment (MoCA), sleep evaluation according to PD sleep scale (PDSS-2), a complete ophthalmic exam, color vision test, best-corrected visual acuity, refraction and Spectral-Domain Optical Coherence Tomography (SD-OCT) imaging..

Results: The rod-mediated maximal percentage of pupil contraction (PPC) was significantly lower at central and peripheral retinal locations in PD patients compared with controls (all $p<0.04$). Cone-mediated PPC was less affected. The sustained, intrinsic melanopsin-mediated pupil response recovery (PRP) in the central retina was significantly faster in PD compared to controls ($p=0.01$).

Conclusions: The intrinsic and extrinsic light responses in ipRGCs are differentially affected at central and peripheral retinal locations in PD patients. Chromatic pupilloperimetry is a useful and noninvasive method for exploration of PLR alterations in PD and may prove to be useful for diagnosis and monitoring disease progression.

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Cornea
VOD

Predicting factors for efficacy of corneal collagen cross-linking for pediatric keratoconus

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Purpose: To evaluate predicting factors of success in corneal cross-linking (CXL) for pediatric keratoconus (KC) patients (18 years old or younger) in a single tertiary referral center.

Methods: Retrospective study comprising pediatric patients who had CXL for KC from 2007 to 2017 with a minimum 1-year follow-up. Univariate and multivariate analysis of the effects of CXL type (Accelerated or Non-Accelerated), demographics (age, gender, background of ocular allergy, ethnicity) and pre-operative LogMAR visual acuity, maximal corneal curvature (Kmax), pachymetry (CCTpre) and refractive cylinder as well as follow-up (FU) time on the final change of Kmax (Delta [Δ] Kmax = Kmaxlast – Kmaxpre) and on the final change in LogMAR visual acuity (ΔLogMAR = LogMARlast – LogMARpre).

Results: 131 eyes from 110 children were included (mean age 16±2 years, range 10 to 18 years). Kmax and LogMAR significantly improved from baseline to last visit: from 53.81 to 52.31 ($p<0.001$) and from 0.23 to 0.19 ($p=0.005$), respectively. Negative ΔKmax was associated with long FU, low CCTpre, high Kmaxpre, high LogMARpre and non-accelerated CXL in univariate analysis. Of those, high Kmaxpre, and non-accelerated CXL were associated with negative ΔKmax in multivariate analysis. Negative ΔLogMAR was only associated with high LogMARpre.

Conclusion: CXL for pediatric KC patients is an effective treatment. Our results showed that the topographic CXL effect is time-dependent and that non-accelerated treatment is more effective than the accelerated protocol. Corneas with advanced disease had greater CXL effect.

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Retina
VOD

Modified Optical Coherence Tomography Imaging Protocol for Retina Clinics During COVID-19 Pandemic

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Purpose: To compare a new rapid “COVID” protocol to the regular Optical Coherence Tomography OCT protocol (“Follow-up” protocol) for managing patients in high volume retina clinics during the COVID-19 pandemic.

Methods: A prospective, double blinded, cross-sectional study was conducted at one academic center. Included were participants with macular edema (ME) who receive Anti-VEGF injections treatment. Two imaging protocols were used: the “Follow-up” protocol (37 B-scans and interscan distance (ISD) of 120 microns) and the “COVID” protocol (13 B-scans and ISD of 240 microns) using Spectralis SD-OCT.

Results: Seventy-nine eyes of 56 patients were included. The “COVID” protocol had a significantly faster mean ±SD acquisition time (4±4.5 seconds) than the “Follow-up” protocol (11±6.3 seconds, p-value<0.0001). The mean ±SD central subfield thickness (CSFT) of the “COVID” and “Follow-up” OCT scan protocols were 297.0±82.6 and 302.8±89.3 microns respectively (p-value=0.311). Values of overall sensitivity and specificity of IRF and SRF were above 84.5%. There was a substantial inter-correlation agreement between two retina specialists and intra-correlation agreement within each retina specialist in evaluating IRF and SRF by both protocols (Kappa values were 0.7-0.8).

Conclusion: The “COVID” protocol is non-inferior to the “Follow-up” protocol for evaluating ME and making a clinical decision when using for follow-up visits in patients who receive Anti-VEGF injection therapy. The importance of this protocol is to reduce patients waiting time and maintain a high standard of care in high volume retina clinics during pandemic time..

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Cornea
VOD

Characterization of LASER-assisted in situ keratomileusis (LASIK) candidates with predicted PTA (Percent Tissue Altered) Index Larger than 40%

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Purpose: To examine which patients that qualify for LASIK surgery as per commonly used dioptric and pachymetric safety limits, would have a predicted PTA (percent tissue altered) value of over 40%.

Methods: Using Excel software we calculated the predicted RST (Residual stromal Thickness) and PTA values of 224 theoretical eyes with spherical equivalent refractive error values of -1D to -14D, and pachymetry values of 450-600µm. RST and PTA values calculations were based on 110µm flap thickness, and 14µm ablation depth for each diopter of refractive error which corresponds to 6.48mm treatment zone. We have filtered the results according to safety limits previously published by the Food and Drug Administration (FDA), American academy of ophthalmology (AAO) and European specialists as well as limits used in our institution. For each filtered list of patients we examined which patients would have a predicted PTA value of over 40% or over 47%.

Results: Out of 224 theoretical eyes, 174 would have qualified for LASIK by FDA-based criteria of MRSE <14 D, RST >250 ¯¼m and a pachymetry value of more than 450 ¯¼m. Sixty-nine of these eyes (39.6%) had a PTA value of more than 40% and 28 (16.1%) had a PTA value of over 47%. Eyes with PTA values of more than 40% had MRSE as low as 5D. All eyes with a PTA value of over 47% had MRSE of 9D or more.

Conclusion: When using common safety-limits, almost half of the patients can have PTA values of more than 40%. Most LASIK treatments which would result in PTA > 40% are of candidates with MRSE of 7D or more.

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Cornea
Live+VOD

Modelling Keratoconus mechanical pathogenesis using finite-element analysis

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Purpose: To model the mechanical pathophysiology of keratoconus using numerical methods.

Methods: Four cornea models were built in Solidwords CAD software, and Finite-element deformation simulation was applied to each one, using Ansys Mechanical Software. The first one was a model of a normal cornea based on previously published biomechanical and geometric data. In the second one, the geometry was unchanged but the elastic properties were altered by diminishing globally Young's modulus value from 0.3MPa to 0.1MPa. In the third model, the elastic properties were normal but the geometry was changed to a keratoconic one, based on a Pentacam Scheimpflug corneal tomographer results of a patient with progressive keratoconus. The fourth one was similar, but using the geometry of the same patientג€™s currently-stable eye.

Results: When applied to the normal cornea, the simulation showed only minor global anterior displacement of the cornea, which was larger when the mechanical properties were altered. No apex displacement occurred and the displacement was symmetrical in all other axes. When applied to keratoconic corneas, asymmetric anterior displacements of up to 220 microns, corneal thinning and apex inferior displacements were seen. Apical anterior displacements were 4 times larger than average displacements in the unstable eye, and 1.5 times larger in the stable eye. Inferior apical displacement were 3 times larger in the unstable eye (30 microns versus 10 microns).

Conclusion: From a certain point, pathological corneal geometry is sufficient for the progression of keratoconus, even when the biomechanical properties of the cornea are normal. Preliminary results of the presented model showed correlation with known clinical findings in keratoconus. Validation of this model using more stable and unstable keratoconus corneas can possibly provide indication about mechanical instability before actual progression occurs, guiding treatment decisions and preventing visual loss.

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Pediatrics
VOD

A Novel Eye-Tracking-Based, Binocular Digital Therapeutic with High Compliance Improves Visual System Performances in Amblyopic Children

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Introduction: The effectiveness of the present binocular amblyopia therapy is often unsatisfactory due to low compliance or unsuitable software and hardware.

Methods: A prospective pilot study was conducted on 20 children aged 4-16 (8.08±3.2„ years) with anisometropic or mixed amblyopia. Subjects watched a movie of their choice 5 times a week for 90 minutes over a period of three months. An eye tracker was used to identify the gaze point of each eye, and dichoptic movies were presented with the foveal area of the non-amblyopic eye blurred to visual acuity 2 lines below the amblyopic eye. The best corrected visual acuity (BCVA) at near and distance, stereoacuity, and reading performance were assessed at each visit.

Results: The mean compliance with treatment dosage was 95%. BCVA improved by 3.34±0.05 ETDRS lines for near (95% CI 0.235-0.375, $p<0.005$) and by 1.8±0.04 for distance (95% CI 0.145-0.257, $p<0.005$) with 6 months of follow-up. Binocular VA improved by 1.1±0.04 and 0.13±0.03 lines for near and distance ($p<0.01$, paired t-test). The mean stereoacuity improved from 285±66 to 73±14 seconds of arc (3 octave steps 95% CI 105-292, $p< 0.005$). Reading speed improved by an average of 40%. No adverse effects were reported; 2 children reported difficulty adhering to the study protocol.

Conclusion/Relevance: Subjects exhibited a significant improvement in visual acuity of the amblyopic eye, stereo acuity, and reading speed. Improvement of binocular VA indicates a reduction in interocular suppression.

The tested Curesight system is a potentially effective home treatment for amblyopia, with high compliance and no difficulty in fitting or calibration, with a year of follow-up.

Relatively Slow Retinal Degeneration Process in a Fam161a Knock-in (KI) Mouse Model for the Human Nonsense Mutation p.Arg523*

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Purpose: The FAM161A-p.Arg523* mutation is the most frequent premature termination codon causing retinitis pigmentosa (RP) in the Israeli Jewish population. Our major aim is to generate and characterize a KI mouse model for this mutation and evaluate its outcome on retinal function and structure.

Methods: Homozygous knock-in (KI) mice with p.Arg373*mutation, which mimics human p.Arg523*, were generated for us by Cyagen Biosciences (www.cyagen.com). Retinal function and structure were examined at the ages of 1, 3, 4.5, 6, 9, 12, 15 and 18 months using electroretinography (ERG), optical coherence tomography (OCT), fundus autofluorescence (FAF) imaging, and histological analysis.

Results: Retinal function determined by ERG, revealed a progressive decrease in amplitudes as compared with WT mice from 1 to 15 months, and the amplitudes resulted in complete flat response during the 18th month. Anatomical structure of the retina, examined by OCT, revealed total loss of outer nuclear layer (ONL) at the age of 18 months, which was first evident at 3 months. Funduscopy examination revealed narrowing of the blood vessels and patchy hyperautofluorescent spots, indicating widespread retinal degeneration. Histological analysis showed progressive loss of photoreceptor nuclei in the ONL but a few nuclei rows were still evident even in relatively old ages.

Conclusions: The outcome of the study evidently indicate that the homozygous p.Arg373* mutation have an impact on retinal function and leads to retinal degeneration in the KI mice. Unexpectedly, the rate of photoreceptor loss in the KI model is much slower than in the FAM161A KO model we previously characterized. We intend to use this model to test novel therapeutic approaches for premature termination codons, such as the nonsense suppressor "Ataluren".

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Oncology
VOD

Characterization of the immunohistochemical profile of benign versus malignant melanocytic conjunctival lesions

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Acquired conjunctival melanocytic lesions are subcategorized into benign lesions such as nevi, potentially malignant lesions, also known as primary acquired melanoses (PAMs), and malignant lesions, melanomas. Usually diagnosis is determined through microscopic analysis by a pathologist. However, due to artifacts in samples or small sample size, a histologic diagnosis is not achieved. In these cases, an analysis of immunohistochemical expression of markers such as P16 is of utmost importance, since different levels of P16 in the different types of lesions can improve our ability to differentiate malignant from benign lesions.
In this study, we characterized the immunological profile by measuring levels of the prime marker P16 in the different types of conjunctival melanocytic lesions. This could improve differential diagnosis (DD), and could help distinguish between benign lesions and malignant lesions that require definitive treatment.

Methods: for the purpose of this study, Formalin-fixed Paraffin-embedded (FFPE) tissue sections of 3 microns were collected from lesions. Tissue samples then were spread on slides. Automated immunohistochemistry was performed using a Benchmark-Ultra slide staining machine (Ventana Medical Systems). Tissue sections then were counterstained using Gillâ€™s hematoxylin protocol, followed by dehydration and cover slipping of slides for microscopic examination. ♀

Results: In the benign nevi melanocytic lesions (n=25) levels of sun damage were minor. The mean expression level of P16 was 64% (64+20.7; P<0.5). In the group of PAM with atypia lesions (n=11) levels of sun damage were moderate, the mean expression level of P16 ♀was 45.45% (45.45%+17.53; p<0.5)

Conclusion: expression of the P16 marker can be of assistance when used as an additional diagnostic tool. It can indicate the aggressiveness of the conjunctival melanocytic lesions from a histopathological perspective. Lower levels of expression is correlated with a higher level of aggressiveness.

Development of a high-throughput screening platform to identify novel therapeutics for DHDDS-related retinitis pigmentosa

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Purpose: The human cis-prenyltransferase complex (hcis-PT) is a heterotetrameric enzyme composed of dehydrodolichyl diphosphate synthase (DHDDS) and Nogo-B receptor (NgBR). By synthesizing the precursor for dolichols, cellular moieties serving as glycosyl carriers, hcis-PT is crucial for protein N-glycosylation. Previously, a missense mutation in DHDDS, identified in Ashkenazi Jews, was shown to result in autosomal-recessive retinitis pigmentosa (arRP). In order to determine the underlying pathological mechanism of arRP at the molecular level, we have recently determined the structure of the complex at atomic resolution and exposed how the DHDDS mutation hinders the catalytic activity. With this structural blueprint, we next sought to identify novel hcis-PT modulators, specifically targeting arRP underlying molecular defects.

Methods: We have established a heterologous expression and purification system for hcis-PT in E. coli cells. Next, we have synthesized a fluorescent substrate analog that exhibits a rise in fluorescence following catalysis, allowing the monitoring of enzymatic activity in real-time. Finally, we have established an orthogonal colorimetric activity assay for hit compounds validation.

Results: First, we established that incubation of the purified hcis-PT with the fluorescent substrate results in a time-dependent rise in fluorescence, correlating with the enzymatic activity. Next, we were able to up-scale the assay for high-throughput screening, currently reaching the functional assessment of up to 384 different compounds in parallel within ~1 hour. With these advancements, we have initiated a drug-screening campaign of ~50,000 different compounds. Initial hits identified using the fluorescence-based assay will be subjected to validation using the orthogonal malachite green assay.

Conclusions: Using an in vitro approach, based on our previous basic research studies, we have established a high-throughput platform to identify novel hcis-PT activity modulators. Our results are expected to provide a steppingstone for the treatment of DHDDS-related arRP and other hcis-PT-related diseases, such as developmental epileptic encephalopathies. Importantly, this work highlights the translational potential of basic biochemical research in ophthalmology, bridging the gap between medical genetics and the development of novel therapeutics.

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Oncology
VOD

Stereotactic Radiosurgery For Intraocular Uveal Melanoma

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Purpose: Uveal melanoma (UM), is usually â€Žtreated by local irradiation (brachytherapy) or by external irradiation â€Žvia different modalities, depending on tumor characteristics. We compared the â€Ž treatment results with fractionated stereotactic radiosurgery (FSR) versus full dose â€Žstereotactic radiosurgery (SRS).â€Ž

Methods: A retrospective chart review of patients who underwent â€ŽFSR/SRS for UM between 2007-2019. Data included demographics, tumor characteristics, response to treatment, side effects, and later sequala. Descriptive statistics were analyzed with JMP statistical â€Žpackage.

Results: Sixty-two UM patients (23 (37.1%) women) were treated with FSR or SRS (34 or 28, respectively). FSR was performed between 2007-2016, while SRS was performed since 2017 and on. 70% of the tumors were choroidal, 22% cilio-choroidal and 8% irido-cilio-choroidal. Two thirds of the tumors were previously treated by brachytherapy, with only 2 (5.9%) primary treatments with FSR vs. 20 (71.4%) with SRS. The mean (±SD) reduction in tumor height and volume was 54.8% (±21.1%) and 32.4% (±26.1%), respectively. There was no statistically significant difference between the reduction in tumor height and volume between primary and secondary treatment ($p>0.2$), although tumors primarily treated by FSR/SRS were larger in height, LBD and volume ($p<0.001$). Tumors treated by FSR lost more height (59.6% vs. 48.9%, one-sided t test $p=0.0472$) and volume (35.8 vs. 28.9%, one-sided t test $p=0.209$) than tumors treated by SRS, but with much longer follow-up (51.6 (±35.4) months (FSR) and 15.2 (±12.5) months (SRS), $p<0.0001$). Local recurrence after FSR/SRS was seen in 5 (8%) cases (6.2% for FSR vs. 10.7% for SRS). 17 eyes (27.4%) developed NVG (38.2%-FSR vs. 14.3%-SRS), resulting in enucleation in 6 (41.2% of them, 9.7% of the entire group, 3 in each treatment group).

Conclusion: Both FSR and SRS provide excellent local control of uveal melanoma as primary and secondary treatments.

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Anterior segment
Live+VOD

Measuring metal trace elements concentration in tears of healthy sheep using Particle Induced X-ray Emission (PIXE) analysis

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Purpose: To measure the concentration of trace elements in the tears of healthy sheep from a homogeneous population and evaluate individual and daily variability in readings.

Methods: Healthy and ophthalmologically-normal female sheep (n=10) of the same breed, habitat and diet, and of similar age, were enrolled. Tears were collected from the left eye of each sheep during five consecutive days (at the same time) using a Schirmer tear test strip without application of topical anesthesia. Concentrations of trace elements in the tears were measured using Particle Induced X-ray Emission (PIXE) analysis. Repeated measures ANOVA was used to test for differences between individuals, between elements and between daily readings.

Results: Mean (±SD) chloride (20550 ±1644 ng/cm2) and sodium (1840 ±153 ng/cm2) concentrations were significantly higher than potassium, sulfur and phosphorus (810 ±130, 818 ±273 and 439 ±211 ng/cm2, respectively) concentrations ($P<0.05$). On the other hand, magnesium (227 ±51 ng/cm2) and calcium (77 ±44 ng/cm2) concentrations were significantly lower compared to other elements. Compared to serum levels, these results suggest active phosphorus transport into tears. There were no significant differences in mean trace element concentrations between individuals ($P=1.0$). Differences between daily readings were detected only in sodium concentration, which increased significantly between days 1 & 5 ($P=0.03$). Iron, silicone and aluminum were not detected in any sample.

Conclusions: In a homogenous population of healthy sheep, there are no significant differences in the concentration of trace elements in tears between individuals, or (with one exception) over time. It remains to be determined whether and how these levels are affected by species, age, gender, habitat, diet, diurnal changes and systemic or ophthalmic diseases.

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Retina
Live+VOD

Activated protein C (APC) and 3K3A-APC inhibition of choroidal neovascularization (CNV) growth is mediated by VEGF reduction.

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Introduction: activated protein C (APC) is a coagulation protease possessing two distinct functions: 1) anticoagulant properties mediated by proteolysis of coagulation factors Va and VIIIa, and 2) cytoprotective effects including antiapoptotic effects, anti-inflammatory effects, neuroprotective effects and endothelial barrier stabilization. A recombinant APC (Xigris®), was approved for the treatment of sepsis, however, therapy was complicated by bleeding events that were considered as drug related side effects. A modified APC, 3K3A-APC, was designed to possess significantly reduced anticoagulant activity (< 10 %) while maintaining full cytoprotective properties, and thus diminishing the risk of bleeding. Our recently published data indicates that APC can inhibit choroidal neovascularization (CNV) growth and leakage in a murine model.

Aim: To study the ability of 3K3A-APC to inhibit CNV development and to evaluate vascular endothelial growth factor (VEGF) levels in CNV lesions upon APC and 3K3A-APC treatment.

Methods: CNV was induced by laser photocoagulation on C57BL/6J mice. APC and 3K3A-APC were injected intravitreally immediately or 4 days following laser injury. CNV development was confirmed in-vivo by fluorescein angiography (FA). CNV area, volume and vascular penetration were evaluated using 3D confocal imaging of FITC-dextran. VEGF levels were measured on choroidal flatmounts and cryosections using immunofluorescence staining with anti-VEGF.

Results: 3K3A-APC treatment inhibited the growth of newly form as well as pre-existing CNV. Volume, area and vascular penetration of CNV from the choroid toward the sensory retina were statistically significant reduced by 3K3A-APC treatment. Elevation in VEGF levels, that was measured in the CNV lesion sites 3-14 days post laser, was significantly decreased upon APC and 3K3-APC treatment.

Conclusions: Our results indicate that the anti-coagulant properties of APC are not mandatory for its ability to inhibit CNV. APC and 3K3-APC exert their protective effects in the retina partially via the reduction of VEGF. Our results warrant further investigation in order to evaluate the potential use of 3K3A-APC as a novel treatment for CNV and other ocular pathologies.

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Generall
VOD

Mucoadhesive polymers enhance ocular drug delivery: Proof of concept study with 0.5% tropicamide in dogs

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Purpose: To assess the efficacy of 0.5% tropicamide following administration of two different mucoadhesive polymers: 1.4% hydroxyethyl cellulose (HEC) or 1.2% hyaluronic acid (HA).

Methods: Eleven healthy dogs were enrolled in the study which consisted of 8 sessions, each separated by a 1-week washout period. At each session, pupillary diameter (PD) was measured using digital calipers every 30 min for 7 hours following drug administration in a randomly-chosen eye. In sessions 1 & 2 PD was measured without drugs (control) and following tropicamide application at time 0 (baseline). In sessions 3-8 PD was measured in eyes that received tropicamide 10 seconds, 1 min and 5 min following application of HEC or HA. Area under the curve (AUC) was calculated using the linear trapezoidal method. Data was analyzed using the linear regression mixed effects model, Mann-Whitney U test and paired Studentג€™s t-test. Normal distribution was confirmed using the Shapiro-Wilk test.

Results: In the baseline group, maximal PD (mean ¸ ± standard deviation 11.120.76 ± ¸ mm) was reached at 2 hours and maintained for 1 hour. Maximal PD was reached earlier, and was significantly greater (P 0.03 ₪‰ג) when HEC was applied 10 seconds (11.920.36 ± ¸ mm at 1.5 hours) and 1 minute (11.90 ¸ ± 0.91 mm at 1.5 hours) prior to tropicamide administration; mydriasis was maintained for 0.5 and 3.5 hours, respectively. Similarly, maximal PD was significantly higher (P 0.04 ₪‰ג) when HA was applied 10 seconds (11.98 ¸ ± 0.62 mm at 2 hours) and 1 minute (11.900.91 ± ¸ mm at 1.5 hours) prior to tropicamide administration. Maximal mydriasis was maintained for 1.5 hours in both sessions. In contrast, PD dynamics did not differ significantly when comparing baseline measurements to tropicamide applied 5 min after HEC or HA (P 0.07 ¥‰ג). AUC increased in sessions 3-8, though differences from baseline measurements were significant only when tropicamide was applied 1 min after HEC (19.640.95 ± ¸ mm*h and 33.930.78 ± ¸ mm*h, respectively, P = 0.006).

Conclusions: The efficacy of tropicamide was enhanced by prior administration of a mucoadhesive polymer. The best results, expressed as greater and longer-lasting mydriasis, were seen when tropicamide was administered 1 min after HEC or 10 sec after HA. Additional studies are needed to determine if HEC & HA of varying concentrations can similarly extend and potentiate the effect of other topical ophthalmic drugs.

The neuroprotective effect of sildenafil in a mouse model of acute intraocular pressure elevation

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Purpose: To examine retinal ganglion cell (RGC) survival in a mouse model of acute increased intraocular pressure (IOP), and the possible neuroprotective effect of sildenafil.

Methods: 1. Microbeads were injected into the right eyes of 30 wild type (WT) mice, which were divided to a single 0.08 mg IP sildenafil injected group (n=22) and a control group (n=8).

2. IOP was measured repeatedly for 21 days.
3. Histological analysis on day 21 was performed for retinal thickness, RGCs count and axonal loss. Molecular markers of inflammation (CD45, TGF²-), stress (SOD1, STAT3), and apoptosis (TNF-±, BAX, BCL2) expression levels were measured by PCR in the retinas and optic nerves.

Results: Following intracameral microbeads injection an acute rise in IOP was demonstrated on day 7 (13±1.87mmHg), with a gradual return to baseline on day 21 (9±0.82mmHg). RGC numbers decreased in the study versus control eyes (20.72 vs 22.61, p=0.05). Following sildenafil treatment, RGC preservation was noted and no statistically significant difference was found between treated and control eyes (21.64 vs 21.25). In the sildenafil treated group, retinal markers showed lower levels as compared to the control group in BAX (0.97 vs 1.44 fold), CD45 (1.19 vs 5.45 fold), and SOD1 (0.52 vs 1.25 fold); higher levels in TGFβ (4.42 vs 1.16 fold), and TNFα (2.91 vs 1.38 fold); and maintained similar levels of STAT3 (2.10 vs 2.15 fold). Additionally, in the sildenafil treated group, optic nerve markers showed lower levels as compared to the control group in STAT3 (0.75 vs 1.17 fold) and TGFβ (0.69 vs 0.98 fold); higher levels in BCL2 (2.31 vs 1.19 fold) and CD45 (1.72 vs 1.12 fold); and similar levels in BAX (1.17 vs 1.31 fold), SOD1 (0.75 vs 0.89 fold), and TNFα (1.96 vs 2.15 fold).

Conclusions: A mouse model of acute elevation of IOP is characterized by a mild to moderate RGCs loss associated with changes in inflammatory, apoptosis and stress related gene expression. Sildenafil has a potential neuroprotective effect on RGC survival demonstrated histologically as well as molecularly by increased BCL2/BAX ratio.

Ocular Surface Temperature Differences in Glaucoma

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Purpose: Accumulating evidence suggests that neuroinflammation and immune response are part of the sequence of pathological events leading to optic nerve damage in glaucoma. Changes in tissue temperature due to inflammation can be measured by thermographic imaging. We investigated the ocular surface temperature (OST) profile of glaucomatous eyes to better understand the pathophysiology of these conditions.

Methods: Subjects diagnosed with glaucoma (primary open angle glaucoma [POAG] or pseudo exfoliation glaucoma [PXFG]) treated at the Sam Rothberg Glaucoma Center (11/2019-11/2020.) were recruited. Healthy subjects with no ocular disease served as controls. The Therm-App thermal imaging camera was used for OST acquisition. Room and body temperatures were recorded, and the mean temperatures of the medial cantus, lateral cantus, and cornea were calculated with image processing software.

Results: Thermographic images were obtained from 52 subjects (52 eyes: 25 POAG and 27 PXFG) and 66 controls (66 eyes). Eyes with glaucoma had a significantly a higher OST compared to controls (mean $0.9 \pm 0.3^{\circ}C$, $P < 0.005$). The difference between the 2 groups remained significant after adjustment for age, sex, intraocular pressure (IOP) and room and body temperatures. Lens status and topical IOP-lowering medication did not significantly affect OST. A subgroup analysis revealed that the OST was higher among eyes with POAG compared to eyes with PXFG, but not significantly.

Conclusions: Differences in the OST between glaucomatous and normal eyes strengthen current thinking that inflammation affects the pathophysiology of glaucoma. Longitudinal studies are warranted to establish the prognostic value of thermographic evaluations in these patients.

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Genetics
Live+VOD

Diverse and complex ocular phenotype caused by novel RBP3 nonsense mutation and ABCA4 splicing mutation

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Purpose: Unraveling the molecular basis of infantile severe myopia and impaired night vision in three siblings of a consanguineous kindred.

Methods: Affected individuals underwent ophthalmologic examination, including electroretinography (ERG) and ocular coherence tomography (OCT). Genome-wide linkage analysis and homozygosity mapping were undertaken using single nucleotide polymorphism microarrays and HomozygosityMapper software. Whole exome sequencing (WES) was performed for one of the patients and for an unaffected family member. Exome data were analyzed using Ingenuity Variant Analysisλ„¢ software and in-house WES data of 500 controls. The mapping and WES results were combined, delineating a few variants possibly associated with the disease. Sanger sequencing and restriction fragment length polymorphism were used for segregation analysis of the variants within the family and for testing healthy ethnically-matched controls.

Results: Three siblings (2 females and a male, ages 14, 12, 4 years) presented with high myopia since infancy (spherical equivalent between -13.00 and -22.50 diopters) and fundus changes compatible with myopia. Only one of the siblings, the 12-y old girl, complained of nyctalopia. ERG responses were diminished and confirmed retinal dystrophy in all three siblings, but in the 12-y old the deficit was more severe.

Exome data were narrowed down to two variants: a novel homozygous duplication mutation in RBP3 (Retinol-binding protein 3; NM_002900.2; c.1687dupA, p.T563fs*5) was found in all three siblings. The duplication leads to premature termination codon (PTC) and possibly to Nonsense-Mediated Decay (NMD). In addition, a previously reported homozygous splice site mutation in ABCA4 (ATP-binding cassette, subfamily A, member 4; NM_000350.3; c.5460+1G>A) was identified only in the 12-y old. The splicing mutation is predicted to cause an in-frame insertion.

Conclusions: The diverse ocular presentation in this family results from a combination of mutations in two genes associated with retinal dystrophies: a novel duplication mutation in RBP3 leading to frameshift, PTC, and possibly NMD, and a splice site mutation in ABCA4. Coexistence of mutations in the two genes in the 12-y old girl likely causes her severe disease, possibly due to additive or synergistic effects of the pathogenic variants in the two genes.

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General
VOD

LONG-TERM EXPERIENCE WITH TUMOR NECROSIS FACTOR-¯± INHIBITORS IN THE TREATMENT OF REFRACTORY NONINFECTIOUS INTERMEDIATE, POSTERIOR OR PANUVEITIS

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PURPOSE: To study the efficacy and long-term effects of Tumor necrosis factor-¯± (TNF) inhibitors in patients with active non-infectious intermediate, posterior or panuveitis (NIPPU) refractory to conventional immunomodulatory treatment (IMT).

METHODS: Retrospective review of medical charts of patients.

RESULTS: Included were 61 patients (104 eyes) of whom 34 were males (55.74%). Mean age at time of diagnosis of uveitis was 26.5 years±16.14 (range 4 to 67 years). Thirteen patients had intermediate uveitis (21.31%), 33 had posterior uveitis (54.10%) and 15 had panuveitis (24.59%). Ocular inflammation was effectively controlled in 87 eyes (83.65%). In 57 patients (93.44%), inflammation was controlled with the first biologic agent. Adalimumab was instituted in 47 patients (77%) while infliximab was used in 14 patients (23%). Mean total follow-up time was 5.5 ±3.43 years (range 1.9 – 11 years) while mean follow-up time after baseline was 40 ±34.08 months (range 3-132 months). Average number of flares per eye in the year preceding start of biologic therapy was 1.5 ±1.1 and it decreased to 0.08 ±0.29/year in the first year of follow-up after baseline. Mean interval between the start of conventional IMT and the institution of biologic therapy was 25.9±30.52 months (range 2- 116 months). In all patients, the indication to start biologic treatment was incomplete response to conventional IMT. Mean logMAR best corrected visual acuity (BCVA) at baseline was 0.42 ±0.65 it and remained stable at last follow-up at 0.40 ±0.69. Mean prednisone dose at baseline was 25.5±20.8 mg/day and it decreased to 7.8 ±9.7mg/day by 6 months (p=0.03). The most common complication at baseline was cystoid macular edema in 19 eyes (18.27%) and it resolved at a mean of 8.4 ±8.8 months. After initiation of biologic therapy 50 eyes (48.07%) experienced flare, median time to first flare was 12 ±9.05 months (range 1-48 months), of these, 35 eyes (70.0%) were being treated with Adalimumab and 15 eyes (30%) with Infliximab. Treatment failed in 6 eyes (5.77%) of 4 patients of whom 2 were treated with adalimumab and 2 with infliximab.

CONCLUSIONS: Treatment with TNF- ¯± inhibitors allowed marked reduction in the prednisone dose while preserving visual acuity over an extended follow-up period. With them, disease control was achieved in 87 eyes. In the majority of patients, the first biologic agent controlled the disease with no need to switch to another biologic agent.

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VOD

YAP is essential for corneal stem cell function and dedifferentiation

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Purpose: To investigate the role of YAP and its regulation in corneal epithelium.

Methods: The expression of YAP was explored in the adult human/murine cornea in vivo by immunohistochemistry and in primary human limbal stem cells (LSCs) before and after differentiation followed by immunofluorescent staining and Western blot analysis of stemness/differentiation gene. YAP was knocked down by silencing RNA and the effect on stemness/differentiation gene expression and stem cell clonogenic potential was explored. Modulation of YAP localization by substrate stiffness was assessed by seeding LSCs in PDMS gels of stiffness comparable to that of human limbus (soft 8kPa) and cornea (stiff 20kPa) and treating with inhibitor (blebbistain) or activator (Rho-activator) of mechanotransduction. Finally, role of YAP in stemness, wound healing and dedifferentiation was checked by sub-conjunctival injection of YAP inhibitor verteporfin.

Results: We show that YAP is essential for corneal epithelial stem cell function. YAP was nuclear in expression in the stem cell compartments of the human and murine cornea in vivo and in undifferentiated human limbal epithelial stem cells in vitro whereas its expression was cytoplasmic in the differentiated cells. Importantly, knock down of YAP induced robust cell differentiation and drastically decreased long-term colony forming potential of LSCs. YAP expression was predominantly nuclear in soft substrate and cytoplasmic in stiff substrate. Inhibition of mechanotransduction in stiff substrate led to nuclear YAP retention and prevented differentiation. In line, forced activation of mechanotransduction in soft substrate led to cytoplasmic localization of YAP and induced differentiation. Finally, inhibition of YAP activity in-vivo led to differentiation of LSCs, delayed wound healing response and prevented proper dedifferentiation.

Conclusions: Altogether, we propose that YAP pathway and its regulation by substrate stiffness is an essential regulator of corneal stem cell function while mutations in YAP or alteration of corneal substrate stiffness may disrupt epithelial regeneration, leading to loss of corneal transparency and blindness. A better understanding of the molecular network controlled by YAP will shed light on LSC self-renewal pathways and will potentially be harnessed into novel therapeutic approaches for corneal pathologies.

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Modeling and Rescue of Genetic Limbal Stem Cell Deficiency

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Purpose: To investigate the role of P63 in limbal stem cell regulation and deficiency

Methods: We generated two conditional P63-L514F mouse models. To assess the gross eye phenotype, we utilized bright-field microscopy of mice aged 2 weeks to 1.5 years old. To examine the corneal structure, we performed H&E staining of histological sections. To unravel the altered pathways in mutant, we performed RNA-sequencing of corneal epithelium. We explored the expression of stemness and differentiation markers by immunofluorescent (IF) staining. To assess the proliferative capacity in vivo, we performed a short EdU pulse. To study the stem and progenitor cell dynamics, we crossed the P63-L514F mouse model with Confetti mouse model and assessed the clonal growth properties and division mode of mutated cells, both in homeostasis and following corneal injury. To examine the therapeutic potential of PRIMA-1MET, we applied eyedrops and performed sub-conjunctival injections during homeostasis and following corneal injury.

Results: P63L514F/+ mice displayed multiple eye abnormalities that are reminiscent of defects found in patients who carry the same mutation, hallmarked by neovascularization and loss of corneal transparency. Furthermore, mutant mice showed impaired wound repair. RNAseq analysis revealed enrichment of pathways related to mucus secretion, vascularization and immune response. In line, histological analysis showed thickening of the corneal epithelium and presence of goblet cells. IF stainings showed altered expression of limbal markers, abnormal expression of conjunctival markers and enrichment of immune cells in the cornea. In addition, mutated corneal cells displayed significantly higher proliferative capacity. Analysis of the properties of confetti labeled mutant clones displayed abnormal size, orientation and survival. PRIMA-1MET alleviated the inflammation in homeostasis and enhanced the wound healing.

Conclusions: Altogether, we propose that P63 plays a key role in regulating corneal morphogenesis and that P63-related pathology involves a developmental failure. In addition, this study demonstrates that limbal stem/progenitor cell state is controlled by P63 while mutations in P63 disrupt epithelial homeostasis, leading to loss of corneal transparency and blindness. Furthermore, PRIMA-1MET showed a promising therapeutic potential in patients.

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SD-OCT evaluation of cRORA progression and its correlation with baseline characteristics

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Purpose: To quantitatively evaluate the long-term progression rate and the baseline predictors of progression of complete retinal pigment epithelium and outer retinal atrophy (cRORA) in cases of dry age-related macular degeneration (AMD).

Methods: Two ophtalmologists retrospectively annotated cRORA. Two-thirds of the scans were annotated by one grader and validated by a second grader. A third of the scans were independently annotated by both graders.

Primary outcomes were: 1) cRORA area progression rate (mm2/year); 2) cRORA square root area progression rate (mm/year); and 3) radial progression rate towards the fovea (mm/year). Secondary outcome was the evaluation for a difference in radial progression in 8 other directions.

The effects of the different baseline predictors on the primary outcomes were also analyzed, including: 1) the total area; 2) area at a diameter of 1 mm around the center; 3) focality; 4) circularity; 5) total lesion perimeter; 6) minimal feret (Feretmin); 7) maximal Feret (Feretmax); 8) minimal distance from the center at baseline; 9) sex; 10) age; 11) presence of hypertension and 12) lens status.

Results: cRORA was annotated in 74 OCT scans from 16 patients with dry AMD, comprising a dataset of 37 baseline and follow up pairs. Inter-grader variability was tested on 1989 standalone OCT B-scans and resulted in a DICE coefficient of 0.75±0.16.

Mean area progression rate was 1.34±0.80 mm2/year (p<0.0001). Mean square root area progression rate was 0.32±0.18 mm/year (p<0.0001). Mean radial progression rate towards the fovea was 0.06±0.12 mm/year.

A multiple variable linear regression model (adjusted r2=0.665) showed baseline focality (estimated 0.101=²-; p=0.0008) and baseline circularity (estimated 1.789-=²-; p=0.0076) were significant factors associated with cRORA area progression rate.

The lesions baseline minimal distance from the center correlated with radial growth rate towards the center on univariate linear regression analysis (p<0.0001;r=0.686).

Conclusion: This study quantitatively measured cRORA area progression rate in dry AMD patients, as compared to traditional fundus autofluorescence measurements. cRORA area progression varied with respect to baseline focality and circularity indices. Radial progression correlated with lesionâ€™s baseline minimal distance from the center. These results may be used in the research of treatments for retinal atrophy secondary to dry AMD.

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Efficacy and possible advantage of mini-scleral and scleral contact lenses over a period of twenty four months in severe dry eye

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Purpose: To evaluate the possible advantage of scleral versus mini-scleral lenses and their respective efficacy in the rehabilitation of the cornea in severe dry eye over a period of twenty four months.

Methods: This study included 37 eyes of patients with severe dry eye. Their ages were 48±14 years, 58% women. The patients were divided into two groups, one group (10 patients) was fit with mini-scleral lenses and the second group (9 patients) was fit with full scleral lenses. Almost half (42%) of the patients had punctal plugs inserted prior to this study and they were divided equally between the two groups. The most common diseases of these patients were sjogren syndrome (7 patients), graft-vs-host disease (3 patients), ocular cicatricial pemphigoid (2 patients). The rest of the patients suffered from dry eye not a result of systemic disease or from medication intake. One patient was fit only unilaterally due to extreme dryness after treatment for primary acquired melanosis (PAM).

Evaluations of visual acuity, corneal staining and conjunctival staining were conducted at baseline and at 24 months.

Results: There was a statistically significant decrease in corneal staining from 2.45 ± 1.54 to 1.03 ± 1.13 ($P<0.05$) based on the oxford scheme for grading ocular surface staining. The best-corrected visual acuity improved from 0.53 ± 0.29 to 0.74 ± 0.31 ($P<0.05$). There was no statistically significant reduction in conjunctival staining from baseline. This study did not show a clinically significant advantage to the full-size scleral lens above the mini scleral in either corneal staining or visual acuity. At the 24 months follow up 63.15% of the patients reported that they had discontinued lens wear primarily due to protein and mucin deposits.

Conclusions: Mini-scleral and scleral lenses are efficacious and well tolerated for use in severe dry eye syndrome up to 16 months. Though full scleral contact lenses afford a larger reservoir, they also seemed to attract more deposits. The full scleral contact lens was not superior to mini-scleral contact lens in reducing corneal staining or improving visual acuity.

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Nd:YAG Capsulotomy Is Not a Risk Factor for Retinal Detachment after Phacoemulsification Cataract Surgery

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Purpose: To evaluate the cumulative incidence and risk factors of pseudophakic retinal detachment (PRD) following phacoemulsification cataract surgery.

Methods: Cataract surgeries performed between the years 2007 and 2016 at the Ophthalmology Unit of Kymenlaakso Central Hospital, Kotka, Finland were included. The cumulative incidence of PRD was estimated through Kaplan-Meier analysis. Patient mortality was incorporated as one of the censoring events. Cox regression analyses were used to evaluate potential risk factors, including age, gender, intraocular lens (IOL) power, and previous neodymium-doped yttrium aluminum garnet (Nd:YAG) laser capsulotomy.

Results: A total of 17.688 eyes of 12.003 patients were included. The mean patient age at surgery was 75.2 ± 9.1 years with 63.5% females (n = 11,228). During the mean follow-up time of 4.3 ± 2.7 years, 83 laterality matched PRD were registered (incidence 0.11% per year). Univariate analyses showed that age (HR 0.93; 95%CI 0.92–0.95), male gender (HR 3.99; 95%CI 2.52–6.33), and IOL power (HR 0.86; 95%CI 0.83–0.90) were significantly associated with PRD (P<0.001 for all) and remained significant in a multivariate analysis. Neither univariate (HR 1.45; 95%CI 0.82-2.54, P=0.201), nor multivariate (HR 1.03; 95%CI 0.57-1.88, P=0.919) analyses showed any association between Nd:YAG capsulotomy and PRD

Conclusions: Male gender, low IOL power and younger age were confirmed as risk factors for PRD after phacoemulsification surgery. Real-world evidence suggests that Nd:YAG capsulotomy does not increase the risk for PRD.

Characterization of the immunohistochemical profiles of basosquamous cell carcinoma vs. basal cell carcinoma and squamous cell carcinoma

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Purpose: To characterize the immunohistochemical (IHC) profile of basal cell carcinoma (BCC), squamous cell carcinoma (SCC) and basosquamous cell carcinoma (BSCC) allowing for IHC as an adjunctive tool for the diagnosis of BSCC tumors.

Methods: We conducted a retrospective study in which analyses of patient files and tissue biopsies were obtained from the Emek Medical Center Institute for Pathology and Cancer Research archives. 38 cases of metatypical basal cell carcinoma (basosquamous cell carcinoma), 39 control cases of basal cell carcinoma, and 39 control cases of squamous cell carcinoma, all from the face, scalp and neck area, were analyzed between 2012 and 2017 resulting in a total of 116 cases.

Tissue microarrays for each subject were assessed for the following IHC markers: BerEP4, cytokeratin 14 (CK14), cytokeratin 17 (CK17), cytokeratin 5/6 (CK5/6), p63 and p53. The percentages of cells that stained positively by each stain for the BSCC, BCC and SCC tissue samples were compared using the Mann-Whitney Test. BSCC to SCC and BSCC to BCC comparisons were made in order to find a panel of IHC markers that may differentiate between the three tumor types.

Results: Eyelid involvement was recorded in 5/38 (13.2%), 5/39 (12.8%) and 4/39 (10.3%) of cases in the BSCC, BCC, and SCC groups, respectively. In the BSCC group, there were 24 (63%) males, 14 (37%) females and the mean age was 67 (range 50-74). In the BCC group 22 (56%) were male, 17 (44%) females with a mean age of 66.5 (range: 53-78). In the SCC group there were 20 (53%) males, 18 (47%) females and the mean age was 68 (range 49-77).

BerEP4 was statistically significant in discriminating between BSCC and BCC (60.5% and 97.4%, $p<0.0001$) as well as between BSCC and SCC (60.5% and 12.8%, $p<0.0001$). Additionally, CK17 differentiated between BSCC and SCC (97.4% and 66.7%, $p<0.0001$). P53 also showed a statistically significant difference between BSCC and BCC (76.3% and 35.9%, $p<0.0001$). No statistically significant difference was observed between the tumors with the remaining IHC stains: CK14, CK5/6 and p63.

Conclusion: It is possible to effectively differentiate between BSCC, BCC and SCC utilizing IHC stains such as BerEP4, p53 and CK17, which have demonstrated a unique response to BSCC. Further research is necessary to determine whether these findings may aid in the accurate treatment of these tumors.

Diplopia from abducens nerve paresis as a presenting symptom of COVID-19: a case report and review of literature

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Purpose: To report a case of COVID-19 and transient abducens nerve paresis, to raise awareness of cranial neuropathies in infected patients even without typical respiratory symptoms.

Methods: The data in the current case was obtained from the Emek Medical Center records. A literature search was performed and included a systematic review utilizing the PUBMED databases based on the combination of search terms: “diplopia” OR “ophthalmoparesis” AND “SARS-CoV-2” OR “COVID-19”. Case history: A 44-year-old febrile man referred for ophthalmologic consultation presented with double vision and headache two days after initial symptoms of fatigue, generalized muscle weakness, and loss of appetite. The patient had no known medical or ocular history, medications, or allergies. Blood tests demonstrated mild lymphopenia (1.28X109/L), elevated C-reactive protein (92 mg/L), and D-dimer (1.3 ug/ml), consistent with COVID-19. Lung auscultation and chest x-ray indicated a bilateral pneumonia-like illness, which was asymptomatic. He subsequently tested positive for SARS-CoV-2. Head CT showed no pathological findings. Ophthalmologic examination revealed binocular diplopia and a limitation to abduction in the left eye, without additional cranial nerve involvement. Pupillary response, anterior pole, and dilated fundus exam was unremarkable. Neurological examination was normal. Lumbar puncture and magnetic resonance imaging were not performed due to resolution of symptoms. Treatment was according to the local infectious disease protocol. The patient was discharged and ten days later was negative for SARS-CoV-2.

Results: Here we describe a case of unilateral abducens paresis as the sole ocular abnormality in a generally healthy male with mild COVID-19. Across recent COVID-19 studies, one patient presented with partial third nerve palsy and accompanying bilateral sixth nerve palsy, one with complete third nerve palsy only, one with bilateral sixth nerve palsy, and two with unilateral sixth nerve palsy. In one study, diplopia as a symptom of COVID-19 has been linked to ophthalmoparesis and Miller Fisher Syndrome, a demyelinating inflammatory polyneuropathy.

Conclusion: Physicians should be aware that patients with COVID-19 may present with cranial nerve involvement even in mild cases without typical respiratory symptoms. Further research is necessary to determine whether persistent sixth nerve palsy or additional third nerve palsy may be correlated with greater disease severity.

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Cornea
Live+VOD

Occurrence of Herpes viruses in morphologically normal corneal grafts

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Purpose: To discover the occurrence of Herpes Simplex Virus (HSV) type 1, 2 and Varicella Zoster Virus (VZV) DNA in transplanted corneas using polymerase chain reaction (PCR), and to determine the relationship between latent HSV-1 and VZV with occurrence of herpetic eye disease in recipients and graft failure.

Methods: 88 corneas were morphologically evaluated before surgery by slit lamp examination and CellChek® specular microscopy. Excluded corneas were tested positive for HBV, HCV and HIV by donor serological assessment, a low cell count (under 2,300 cells /mm2), corneal scars and abnormal endothelial cell morphology. Transplanted corneas were directly sampled for HSV 1,2 and VZV DNA by PCR. All eyes transplanted with the donor corneas were evaluated and followed for corneal transparency, endothelial cells morphology and number/mm2 by specular microscopy, signs for ocular inflammation, intraocular pressure, and anterior segment optical coherence tomography (OCT) for graft attachment.

Results: HSV-1 DNA was detected in five transplanted corneas out of the 88 that were examined (5.7%). HSV-2 was not detected in any cornea, and VZV in one cornea out of 82 examined (1.2%). Four of the positive corneas were used in descemet membrane endothelial keratoplasty (DMEK) surgeries. One for a combined DMEK/anterior vitrectomy/ iridoplasty surgery and one as a tectonic graft. One recipient (16.7%) developed herpes dendritic epitheliopathy and keratouveitis 12 months after transplantation although the graft remained clear after treatment. One cornea was used for a tectonic graft and stayed edematous at 20 months follow - up. The rest of the corneas stayed clear.

Conclusions: Herpes viruses, especially HSV-1, may be PCR DNA positive in morphologically normal donor corneas. Recipients of herpes positive corneal grafts may be at risk for herpetic eye disease. Further evaluation with a bigger sample size and a longer follow-up time is needed to establish a clinical correlation to donor graft survival and to recipient ocular infection with HSV-1. HSV-1 positive DNA samples will be evaluated for viral RNA by reverse transcriptase PCR (RT-PCR) to further evaluate HSV latency and active replication.

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General
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Evidence-Based Medicine In The Field of Ophthalmology In The Age of the COVID-19 Pandemic

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Purpose- Use of evidence-based medicine (EBM) has become fundamental to any practicing clinician; however, building a body of evidence requires time. Moreover, the need to rapidly acquire and publish information about the new COVID-19 pandemic inevitably caused a shift away from the paradigm of evidence-based medicine (EBM). We sought to describe this shift.

Methods- We conducted a literature search for all publications in the field of Ophthalmology pertaining to COVID-19. The search was conducted on 15/9/2020 using Pubmed and Scopus databases, and only publications in English were included. Each publication was graded according to a widely accepted Center for Evidence Based Medicine Levels of Evidence table. Publications were graded between 1 for highest level of EBM (for randomized controlled trials and meta-analyses) and 5 for lowest level of EBM (for expert opinion and bench research). Where available, we recorded time (in days) between submission and publication, and whether any revisions were required.

Results- Our search yielded 335 publications that were included in the study. We found that 322 (96.1%) were of lower level EBM, and only 13 (3.9%) were of EBM level 3 or higher. Trend over time was for higher levels of EBM to appear later on in the pandemic. In fact, none of the higher levels EBM publications appeared before the month of May. Average time between submission and publication was 19.9±20.2 days, with 34.9% of publications accepted without revisions.

Conclusions: Our findings indeed suggest that information published in the early stages of the pandemic were of lower level EBM, and as expected higher levels of EBM require time. Clinicians need to be aware that in a rush to publish as fast as possible, quality standards may have been compromised. We therefore suggest that appropriate care should be taken when deciding to assimilate data published in the early stages of any event into our daily practice.

Parameters affecting chord mu and angle alpha in cataract surgery candidates

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Purpose: Previous studies recently showed that biometry measurements factors as high values of chord mu and angle alpha are associated with impaired visual quality after multifocal intraocular lens implantation (MF-IOL) during cataract surgery. In this study, we aimed to identify factors affecting chord mu and angle alpha measurements.

Method: Ocular biometry measurement results of consecutive 2877 cataract surgery candidates were retrospectively analyzed. Biometric measurements were performed using IOL-master 700 device. This device measures chord mu length and angle defined by the displacement of the visual axis compared to the pupil. We defined also this displacement compared to iris center as chord alpha length and chord alpha angle. In this study, we analyzed the influence of others biometric parameters on these values.

Results: 462 eyes were excluded due to incomplete demographic data, low quality exam or previous ocular surgery. 2415 eyes were included. The mean chord mu and chord alpha length were 0.35±0.22 and 0.49±0.21, respectively. Chord mu length was found to be moderately associated with chord alpha length (Pearson Corr.: r=0.641, p<0.01). A weak and negative correlations between chord mu length to axial length (AL) and anterior chamber depth (ACD) were found (r=-0.114, r=-0.186 respectively, p<0.01) and positive correlation with pupil size (r=0.160, p<0.01). A negative correlation was also found between chord alpha length to AL and ACD (r=-0.218, -0.203 respectively, p<0.01) but was not correlated with pupil size. Chord mu length increased with pupil size whereas chord alpha length stayed stable. Chord mu length average was 22% higher in patients with dilated pupils of 7-8mm compared to patients with non-dilated pupil of 2-3mm (p<0.01). 222 patients (9.2%) had a high chord mu length (> 0.6mm). After correcting for pupil size by linear regression, 21% of these patients were defined as high chord mu due to of dilated pupil.

Conclusions: Chord mu and chord alpha lengths are closely related values. They decreased with higher AL and higher ACD but only weak correlations were found between these parameters. Additionally, chord mu length slightly increased with pupil size whereas chord alpha was stable. Interpretation of chord mu length of patients after pharmacologic mydriasis has to be done with caution before MF-IOL implantation to prevent erroneous exclusion of suitable patients. Chord alpha length could eventually be a potential substitute for these patients.

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Genetics
Live+VOD

Isolated keratoglobus - Inheritance pattern and molecular analysis of three families

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Abstract

Purpose: Keratoglobus is a rare corneal disorder characterized by generalized thinning and globular protrusion of the cornea. Affected individuals typically have significantly decreased vision and are at risk of corneal perforation. The genetic basis and inheritance pattern of isolated congenital keratoglobus are currently unknown.

Methods: Case series and molecular analysis: Whole-exome sequencing and direct Sanger sequencing, expression analysis by qPCR, splice-site variant analysis, and immunohistochemical staining.

Results: Three unrelated non-consanguineous families diagnosed with Keratoglobus. Four patients from three families had clinical findings consistent with keratoglobus including globular protrusion and thinning of the corneas, more prominent at the periphery, and high astigmatism. We identified bi-allelic truncating and splice site mutations in a novel gene which fully segregate with the disorder. We have also confirmed the expression of the gene in the human cornea by RT-PCR and immunohistochemical staining.

Conclusions: Our results suggest that isolated congenital keratoglobus is an autosomal recessively inherited disorder associated with variants in a novel gene.

Sema3A Antibody for Neurodegenerative Diseases of the Optic nerve

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Purpose: To create an Antibody to block the apoptotic program of Semaphorin3A

Sema3A is a protein involved in the signal cascade leading to apoptosis of neural cells in CNS.

Methods: We created animal models of optic nerve assaults analog to diseases of optic nerve in human.The antibodies created were evaluated in vitro in neural cells culture and the most potent one, 3H4 ,was loaded in implants which were implanted in the righ eye of rats or rabbits.Four models of optic nnerve and retina were used: complete transection of the optic nerve and retinal detachment in rat and acute glaucoma and NAION in rabbit.Two weeks following assault the retina of all animals was styained retrograde with Di-Asp10.Viable RGC were counted on flat mounted retina.

Results: We succeeded to save 46% -52% of the RGC in the implanted eyes with 3H4.Control injured optic nerves and retina treated with DMEM presented 10%-12% viable RGC of the normal no injured eyes.

Conclusion: The antibody 3H4 was found to be a potent substance that blocks the apoptotic program of Sema3A.

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VOD

Repeatability of corneal mapping measured using a hybrid optical coherence tomographer with Placido topography versus a Scheimpflug tomography

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Purpose: To assess the repeatability of corneal mapping measured using a hybrid optical coherence tomographer with Placido based topography versus a Scheimpflug based tomography.

Methods: This study included 38 eyes of 19 keratoconus patients. Their average age was 27±6.8, and 57% were male. The keratoconus was categorized according to Belin staging system in group one as stage 2 or 3 (ten patients) or group two as stage 4 (nine patients). They were measured using a Scheimpflug based tomography system (Pentacam, Oculus GmBH, Wetzlar, Germany) and with a hybrid OCT and Placido based system (MS-39, Costruzione Strumenti Oftalmici,CSO, Florence, Italy). The patients were all measured at the same time of day in identical environments. None of the patients had undergone any previous procedures or surgeries including cross linking or intra-stromal rings. They instilled no topical medications including artificial tears. The CSO measurements were acquired after a blink and stabilization of the tear film. Five measurements were performed on each instrument and the highest quality measurement as defined by the QS index in the Pentacam and the acquisition quality index in the MS-39 were used for analysis. Repeatability was assessed using coefficient of variation (CoV).

Results: In the keratoconus group one, the CoV was less than 1.63% in both instruments when analyzing central 3 mm keratometry, maximum K, Q value, posterior elevation, pachymetry at the thinnest point and anterior chamber depth. In the keratoconus group two, data from the same measurements was acquired, showing a greater CoV, but still below 2.13%. The repeatability results were lower in both instruments with regard to astigmatism in the severe keratoconus group.

Conclusions: The repeatability of maximum K, Q value, posterior elevation, pachymetry at the thinnest point and anterior chamber depth measurements was high in both the Scheimpflug based tomography and the hybrid OCT and placido based instruments. The repeatability was slightly higher in the keratoconus group one than the keratoconus group two.

Chromatic pupilloperimetry for objective diagnosis and monitoring of optic neuritis

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Purpose: To characterize rod-, cone- and melanopsin-mediated pupil responses (PLR) for small focal chromatic light stimuli presented in peripheral and central retinal locations in optic neuritis patients.

Methods: Ten acute optic neuritis (ON) patients (mean age ± standard deviation: 32.3 ± 9.3 years) 7 females and 3 males, and 26 age-similar healthy controls (35.4 ± 12.4 years, p=0.42) 15 females and 11 males, were enrolled. The pupil light responses (PLR) for small (0.43 degrees) red and blue light stimuli (peak 485 nm and 625 nm, respectively) presented at 54 locations of a 24-2 visual field were recorded. In addition, the melanopsin-mediated sustained pupil responses (percentage of pupil recovery, PPR) were evaluated at central and peripheral VF locations. All patients underwent Optical Coherence Tomography (OCT) imaging, standard perimetry (Humphrey SITA Standard protocol) and their best corrected visual acuity (BCVA) was determined.

Results: Attenuated melanopsin-mediated PPR was recorded in the peripheral VF in ON eyes compared to controls, with ROC AUC = 91.1% (p=0.001). The rod and cone-mediated percentage of pupil contraction (PPC) was lower by more than 2 standard errors (SEs) from the mean of controls in majority of visual field test targets (mean ± SE: 60% ± 12 % and 55% ± 10 % of test targets, respectively) in optic neuritis eyes, even in patients with normal BCVA. Furthermore, even though normal BCVA and VEP P100 were recorded in the fellow eyes, substantially lower rod- and cone-mediated PPC values (lower than 2SEs from the mean of controls) were identified in the fellow eyes of all patients (mean ± SE: 33% ± 9 % and 30%± 7 % of test targets, respectively). Peripapillary OCT of both eyes was within normal limits.

Conclusions: Substantially lower rod- cone- and melanopsin-mediated PLR are recorded in ON and fellow eyes of patients, even in eyes with normal BCVA. The melanopsin-mediated pupil response for blue light at the peripheral retina may present a novel highly sensitive surrogate functional biomarker for detection of ON.

Retinal Degeneration Associated with Mutations in the KIZ Gene

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Purpose: The Kizuna (KIZ) gene encodes a centrosomal protein and was first reported to be associated with inherited retinal dystrophy (IRD) in 2014. Since then only six cases have been reported worldwide. Here we aimed to characterize genotype and phenotype in what to our knowledge is the biggest cohort of patients with KIZ-associated IRD reported to date.

Methods: Medical records of KIZ patients were retrospectively reviewed, and genetic, clinical, imaging and electrophysiological data were analyzed.

Results: We identified 18 patients with KIZ mutations: 16 (ages 13-66) have a homozygous p.R76* mutation and 2 (ages 42&50) were compound heterozygous for p.R76* and c.3G>A (p.M1?). From the homozygous group, 13/16 were of Ashkenazi Jewish (AJ) descent, 2 from Morocco and 1 from Turkey. Both compound heterozygous patients were from a mixed background (Bulgaria-Macedonia and Poland-Iraq) . Clinical data was available for 14 patients: 8/14 patients (ages 21-66) had good visual acuity (≥20/40) in at least one eye up until the last examination and 8/12 patients (ages 25-66) manifested cataracts, commonly posterior subcapsular. Fundus imaging, available in 11 patients, showed two main phenotypes: 6 patients (5 Homo and 1 het, ages 13-66) manifested relatively mild disease with minimal funduscopic changes even at advanced age, although FAF revealed hypoautofluorescent spots and a macular hyperautofluorescent ring. Five other homozygous patients showed more aggressive disease with funduscopic features of classic RP, including bone spicule-like pigmentation, attenuation of retinal vessels and optic disc pallor. On OCT, 4/8 patients (2 mild and 2 with a RP-like phenotype) showed a mild ERM, and only one (in the mild group) had cystoid changes. Visual fields showed progressive constriction, reduced to less than 10 degrees by the age of 30 in 7/9 patients. FFERG was still recordable in patients up until 62 years of age, with a rod>cone dystrophy pattern. Interestingly, the Arden ratio on EOG testing was reduced in all 6 patients who performed this test to values lower than predicted by the extent of FFERG loss

Conclusions: KIZ mutations are an uncommon cause of IRD worldwide, but are not rare among AJ, with a 1:79 carrier rate for the p.R76* mutation. Fundus findings are often mild and can be missed. In an AJ patient, FFERG testing showing a rod>cone pattern of injury and an EOG Arden ratio that is lower than expected may suggest KIZ as the cause of disease.

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Whole Exome Sequencing Results of 520 Patients with Inherited Retinal Diseases

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Purpose: Identifying genes and mutations that cause inherited retinal disease (IRD) can be challenging due to high clinical and genetic heterogeneity. Mutations in over 250 genes are known to cause IRDs and additional genes are being discovered annually. Whole exome sequencing (WES) is a comprehensive technique that allows advanced analyses to identify causal mutations. This study aimed to identify causal genes for a subset of IRD patients from our cohort using WES, present the distribution of the causative genes in the solved samples and estimate the total diagnostic yield of WES for IRDs.

Methods: WES was performed on 520 DNA samples (representing 511 families) at the “3billion” company. Ethics approval was obtained from the Hadassah IRB and participants provided written informed consent. Data analysis was done by “3billion” and the “Genoox”/”Franklin” web-based analysis tool. Variants were validated by PCR and Sanger sequencing.

Results: Disease-causing mutations were identified in 36% (n=188) of the index cases representing 88 different causative genes. The most common genes were USH2A (7%; n=14) and ABCA4 (6%; n=11) while each of the remaining was responsible for less than 5% of cases. Mutations in 45 causative genes were seen in only a single family each. Most of the solved cases (68%; n=128) have not been previously tested by a targeted sequencing panel. Seventeen percent of the unsolved cases (n=54) carried at least one heterozygous recessive pathogenic mutation with no identified mutation on the counter allele. Interestingly, 22% (n=42) of the solved cases carried a heterozygous recessive mutation in an additional IRD gene. The additive value of these results to our general cohort was 9%, bringing the percentage of solved families in our cohort to 69%..

Conclusions: Our results indicate that WES can significantly improve the diagnostic yield for IRDs. Many cases were not previously solved mainly because of low quality panel results and because recently discovered causal genes were not yet included in the panel. Unlike the targeted sequencing panel, WES is not restricted to a specific set of genes- the analysis can easily be modified to include additional genes as they are discovered and can also help identify novel disease-causing genes. Our updated solved cohort data can be used to inform patients about the diagnostic yield of WES in IRDs, enabling informed decisions regarding out-of-pocket funding of WES testing.

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The message in the non-coding RNAs of the mammalian retina

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Purpose: The retina expresses many non-coding RNAs, but the physiological functions and/or relevance of a majority of these are yet to be discovered. A few recent studies suggest that some ncRNAs can produce small open reading frame (smORF) peptides. We aim to identify retinal smORFs and study their function in vivo. This study will shed light on missing components of the retinal proteome and help identify novel mechanisms underlying development and disease.

Methods: Photoreceptors (rods - Nrlp-GFP and S-cone like - Nrlp-GFP;Nrl-/-) were purified from mice retina. Subsequently, RNA was isolated and used for RNA-seq. Novel transcripts were identified by genome guided de-novo assembly using TopHat2 and Cufflinks. Transcriptome assembly and Ensembl annotation (v84) were used to construct a custom database of ncRNAs, which were translated by ORFfinder to generate a list of predicted smORF peptides. Concurrently, total protein was extracted from mouse retina and processed for LC-MS/MS analysis on an Orbitrap Lumos Tribrid mass spectrometer. Peptide spectral data were searched against the predicted retinal smORFs and UniProt protein sequences. Pfam and deeploc were used to predict functional domains and cellular localization. Tblastn was used for phylogenetic analysis.

Results: Retinal transcriptome analysis yielded over 90 thousand potential smORFs, out of which 1936 peptides matching 1813 ncRNAs genes were identified by LC-MS/MS analysis (FDR of 95%). About 46% (828/1813) of identified smORFs come from previously un-annotated ncRNAs. We then performed an extensive bioinformatic analysis of smORFs, predicting functional domains, cellular localization and conservation. Our initial analysis shows that over 1000 of the smORFs show conservation between mouse and human, and contain domains associated with RNA processing (e.g., translation and ribosome), DNA binding and structural elements. In addition, we analyzed Cut&Run data from Nrl and Crx, to identify retina specific regulatory constraints. Additional studies are being performed to validate and functionally characterize a few candidates.

Conclusions: Integration of bioinformatics and proteomic data analysis led to identification of 1936 putative retinal smORF peptides, originating in genes categorized as ncRNA. These findings expand our understanding of both the different components of the genome and the proteome as well as provide a foundation to study the roles of ncRNAs in retinal development and disease.

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Simplifying the diagnosis of optic tract syndrome using oct RNFL

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Methods: Five patients were diagnosed of optic tract injury (OTI) in Bnai Zion medical center between 1/2016 and 1/2020. Data of demographics, surgical procedures, eye exams, and analysis of imaging results including optical coherent tomography (OCT), fundus photos and MRI scans were collected retrospectively from the electronic files.

Results: Three children and two adults were included in this study. Etiologies for OTI were gliomas (4), and one motor vehicle accident. Visual field defects were incongruent (n=5) and complete (n=2) homonymous hemianopia in the contralateral side. VA was good (2) moderate (1) and reduced (2) in one (2) or both eyes. RAPD was detected in 4 of the contralateral eyes. Color vision was intact in 2 and not measured in 1. Fundus exam revealed Bow Tie atrophy in all 5 patients. MRI imaging revealed suprasellar glioma involving the chisam, and tract (2) and also the ipsilateral optic nerve (2), only optic tract (1) and post traumatic OT hemorrhage (1). OCT RNFL demonstrated thinning of the RNFL layer in the nasal and temporal quadrants of the contralateral eye in all cases. The atrophy of superior and inferior fibers of the ipsilateral optic discs were not clearly detected in fundoscopy and OCT RNFL(except for the post-traumatic case). Color fundus photos helped assessing this pathognomonic bow tie palor. When presenting the data with laterality of visual field, fundus photos and MRI imaging, the diagnosis is easily made.

Conclusion: OCT can demonstrate the characteristic atrophy pattern caused by longstanding OTI. Presenting all clinical, radiologic and OCT data, can immediately reveal the laterality and the involvement of the optic tract, even when other structures like chiasm are involved. Optic tract lesion is a rare and confusing diagnosis, and using systematic order of data presentation improving the ability to detect the patterns leading to the correct diagnosis.

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Dense SNP IAMDGC dataset developed through imputation

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Purpose: The International Age-Related Macular Degeneration Genomics Consortium (IAMDGC) published a full genome-wide association study (GWAS) on 16,144 AMD individuals and 17,832 controls of European descent (Fritsche et al., 2016). However, the IAMDGC dataset is multi-ethnic, and many of the participants could not be imputed accurately with the imputation reference panels available at that time. We set out to reimpute the IAMDGC data using the Trans-Omics for Precision Medicine (TOPMed)

Methods: Project imputation panel to greatly improve the density of imputed variants, increase the diversity of the study, and increase the power of the study. 52,189 individuals (30,886 AMD cases, 21,303 controls) were originally genotyped by the IAMDGC including those classified as non-European. Of the 569,645 variants on the genotyped SNP chip, 85,591 variants were used to investigate the ancestry of the individuals via principal components analysis, incorporating2,504 individuals representing 27 ancestries from the 1000 Genomes Project Phase3. Variant filtering and quality control (QC) was performed in the same way as for the original IAMDGC analysis, including screening for variants that differ between whole-genome amplified (WGA) and blood DNA samples, differential missingness or allele frequency, and applying quality control to males and females separately.

Results: QC for the X chromosome was performed using the XWAS software suite. We phased genotype data with Eagle v2.4, and imputed untyped variants using the TOPMed Imputation Server and Minimac4 using the TOPMed v2 reference panel (97,256 reference samples). Successful imputation of 290,889,205 variants on the autosomes and 17,215,853 variants on X was obtained.Subsequent QC filtering resulted in 48,944 samples imputed to 7,788,691 variants with R2≥0.8 and minor allele frequency (MAF)≥0.01, and 18,604,089 variants with R2≥0.3, MAF≤0.01 on the autosomes, and 3,503,046 variants with R2≥0.8 on X. Of these, 1/3 are insertions and 2/3 deletions.

Conclusions: Using this approach, we are investigating rare variants previously unable to be well imputed, as well as using this more accurately imputed multi-ethnic cohort from the original IAMDGC study for further genetic analysis.

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Clinical and optical coherence tomography angiography characteristics of perifoveal exudative vascular anomalous complex

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Purpose: To describe clinical, optical coherence tomography (OCT), and OCT angiography (OCT-A) characteristics of patients with perifoveal exudative vascular anomalous complex (PEVAC).

Methods: Retrospective analysis of demographic data, clinical examination, OCT and OCT-A features, and treatment results of eyes with PEVAC.

Results: Thirteen eyes of 11 patients (3 males and 8 females) were reviewed. Mean age of onset was 70.8 years. Mean follow up period was 33.5 months for eight patients. Hypertension was present in 10 patients (90.9%); hyperlipidemia in 10 patients (90.9%) and diabetic mellitus (DM) without diabetic retinopathy (DR) in 4 patients (36.4%). Four cases were initially misdiagnosed as diabetic macular edema (DME) or neovascular AMD (NVAMD). At presentation PEVAC lesions were detected in all eyes by OCT with intraretinal fluid (IRF) and hyper-reflective foci in all cases, and small drusen in 4 cases (36.4%). In OCT-A, PEVAC lesions were detected in all eyes and were most located in the superficial capillary plexus. All cases were associated with IRF. Five cases had multiple lesions while in eight was single. Central macular density was statistically significant between PEVAC eyes and fellow eyes. Four cases treated with intravitreal injection of anti-VEGF drugs with improvement of visual acuity (VA) and decrease in IRF in three of them. One eye treated with focal laser photocoagulation with full resolution of the IRF.

Conclusion: The present series confirms that PEVAC corresponds to a new entity that differs from other conditions associated with capillary aneurysmal lesions. It must be differentiated from DME and NVAMD. PEVAC can be present in patients with hypertension, AMD changes and DM without DR. PEVAC may respond to anti-VEGF therapy in specific cases.

OCT-A confirmed the presence of the PEVAC in all eyes with a statistically significant difference in the central macular density between PEVAC eyes and the fellow eyes.

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Clinical characterization and genotype-phenotype correlation in RPGRIP1 patients with autosomal recessive early onset retinal degeneration

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Purpose: RPGRIP1 encodes a ciliary protein expressed in photoreceptor cilia. It contains a C-terminal RPGR interacting domain and two C2 domains, which are known to be involved in signal transduction or membrane trafficking. Mutations in this gene are known to cause ~5% of Leber congenital amaurosis (LCA) worldwide, but are also associated with cone-rod dystrophy (CRD) and retinitis pigmentosa (RP) phenotypes. Our purpose was to clinically characterize RPGRIP1 patients in the Israeli and Palestinian populations, perform an extensive literature search to collect clinical data of additional RPGRIP1 patients, and from this combined data set we attempted to identify common clinical features and sought genotype-phenotype correlations.

Methods: Clinical data from 16 patients from our cohort and 175 RPGRIP1 patients previously reported by other groups was collected including (when available) family history, best corrected visual acuity (BCVA), refraction, full ocular examination, ocular coherence tomography (OCT) imaging, visual fields (VF) and full-field electroretinography (ffERG).

Results: Out of 191 patients, the majority (158, 83%) were diagnosed with LCA, 17 (9%) with CRD, and 16 (8%) with RP. Age of onset in all patients for whom this data was reported was during childhood (n=121), all had moderate myopia (n=49, Mean of -4.8D, SEM=0.8), and average BCVA was 0.06 Snellen (n=116; only 10 patients had VA>0.1). On funduscopy, narrowing of blood vessels was noted early in life. Most patients had mild bone spicule-like pigmentation starting in the midperiphery and later encroaching upon the posterior pole. OCT shows thinning of the ONL, while cystoid changes and edema are relatively rare. VF are usually very constricted from early-on. FFERG responses were non-detectable in the vast majority of cases. Most of the mutations are predicted to be null (297 alleles) and 85 alleles harbored missense mutations. Missense mutations were identified only in two regions: the RPGR interacting domain and the C2 domains. Patients with 2 missense mutations tended to show a milder course of disease (CRD/RP and not LCA).

Conclusions: Our results indicate that RPGRIP1 usually causes severe retinal degeneration at an early age, with rapid disease progression. Most patients manifest a LCA phenotype. Missense changes in the conserved domains are usually associated with a less severe disease phenotype (CRD/RP) than null-predicted mutations.

in-vitro and in-vivo characterization of photoreceptor precursors derived using an hESC-CRX-GFP reporter cell line

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Purpose: Retinal degenerative diseases lead to dysfunction and loss of photoreceptor cells (PR), causing visual impairment. Cell-based therapy may serve to support and perhaps replace the failing host PRs. Our purpose was to explore ways to enhance differentiation of Human Embryonic Stem Cells (hESCs) into PR precursors in vitro and to examine their survival and further maturation following subretinal (SR) transplantation in rodent eyes in-vivo.

Methods: The cone-rod homeobox (CRX) gene encodes a key transcription factor of PR differentiation. Using CRISPR-Cas9, we replaced the termination codon of one of two CRX copies by 2A-GFP reporter gene in a hESCs line. The engineered hESCs express the GFP reporter gene under regulation of the endogenous promoter of CRX. We then cultured the hESC-CRX-GFP cells for 3.5-4 months in-vitro with modulatory and trophic factors to derive retinal organoids, and evaluated expression of GFP (CRX) over time.

To further characterize cells, immunocytochemical (ICC) staining was performed. hESC-CRX-GFP cells were then transplanted into the subretinal (SR) space of immunodeficient NSG mice. in vivo examinations included Micron III fundoscopy for GFP visualization, FAF, and OCT imaging. Engraftment, survival, and expression of photoreceptor markers were assessed histologically and by immunohistochemistry (IHC) 4,8 and 12 weeks post-op.

Results: In vitro, at 4 months, >45% of the CRX-GFP hESCs were GFP positive. Staining with anti-Crx antibodies showed co-localization with GFP, confirming this level of expression. Approximately 60% of Crx-positive cells also expressed the photoreceptor marker Recoverin. In-vivo Micron III fundoscopy showed GFP expression up to 12 weeks following SR transplantation of CRX-GFP hESCs, attesting to long term survival. OCT scans showed SR grafts in areas that were GFP-positive, with no evidence of tumor formation. Following enucleation and IHC staining, transplanted cells expressing Crx, Recoverin, rhodopsin and blue cone opsin were identified within the grafts.

Conclusions: To obtain an enriched population of photoreceptor precursors, we generated CRX-GFP reporter hESCs. Following in-vitro culturing for 4 months, a substantial percentage of cells expressed Crx and Recoverin. Following SR transplantation in vivo, CRX-GFP hESCs survive for at least 12 weeks and express additional cone- and rod-specific markers.

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Binocular Temporal Summation in Normally Sighted and Amblyopic Subjects

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Purpose: Binocular summation (BS), the process by which the brain combines the information received from both eyes, is widely studied in the spatial domain. The current research focused on mechanism for binocular summation in the temporal processing domain in amblyopic and normally sighted (NS) subjects. We hypothesized that similar to the spatial domain, the gain-control theory stating that information arriving from one eye exerts gain control over the other is valid in the temporal domain.

Methods: We explored temporal summation by measuring the Critical Frequency Fusion (CFF), using a customized dichoptic system, which generates flickering light at various luminance and inter-ocular phase shift. CFF was measured using the staircase method. In order to assess the relationship between space and time, we have further developed a computerized Flickering Stereopsis test that can test Temporal Stereopsis with various inter-ocular phase shifts. Electrophysiological studies were additionally performed by recording visual evoked potentials (VEP) in response to flickering stimuli.

Results: The CFF was measured in 15 NS and 12 amblyopic subjects under a binocular viewing condition. BS was found in NS subjects at low-luminance flickers, and was degraded upon the addition of a phase shift. In contrast, for the amblyopic subjects, BS was evident only when a small phase shift (of 0.1€) was presented to allow an earlier presentation of the flicker to the amblyopic eye ($p=0.004$) or when increasing the stimuli luminance to this eye ($p=0.0008$). Furthermore, measure of VEP responses (7 NS and 8 amblyopic subjects) revealed a similar trend wherein introducing a phase-shift to NS subjects decreased the response amplitude to binocular stimuli ($p=0.02$), whereas its introduction in amblyopic eye resulted in the increase of the VEP response amplitude ($p=0.01$). An autocorrelation test revealed the low correlation between the subject's waves and a pure sine wave for the amblyopic eye improving upon phase addition. In agreement with these results, introducing inter-ocular phase shifts in the flicker stereopsis test improved the stereopsis performance in the amblyopic subject and degraded it in NS.

Conclusion: Maintaining a balance between the eyes, showed that the gain-control model is also valid in the temporal domain. Further exploration will shed light on the temporal visual system and on the effect of BS enhancement in time, and help develop an effective vision training tool based on temporal characteristics.

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KLOTHO protein retinal expression in diabetic mice and the effect of vitamin D supplementation on its expression

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Purpose: Diabetes Mellitus is one of the most common diseases worldwide. The mechanism of diabetic retinopathy is not fully understood. Klotho is a transmembrane protein with an antioxidant and anti-aging effect. In addition, it is involved in insulin sensitivity. A decrease in Klotho levels was associated with diabetic nephropathy in diabetic patients. The purpose of this study is to evaluate the expression of Klotho protein in type I diabetic mice retina compared to control group of healthy mice, in addition to examine whether early versus late administration of Vitamin D in mice with type I diabetes affects the expression of Klotho in retinal tissue.

Methods: Four groups of DBA/2J mice were included, 7 mice in each group. The first group was the control wild type group, the second group underwent induction of diabetes with Streptozotocin, the third group underwent induction of diabetes along with early Vitamin D supplementation and the fourth group underwent induction of diabetes along with late (three weeks after) Vitamin D supplementation. Eyes from each group were enucleated, and immunofluorescence staining for Klotho protein was performed on retinal sections. Image fluorescence analysis was performed using FIJI ImageJ processing software.

Results: Klotho protein is expressed in wild type DBA/2J mice retina. Fluorescence analysis revealed statistically significant (p=0.033) difference in Klotho retinal expression between the group of diabetic mice (mean fluorescence 175420.61) and the group of diabetic mice with the late intervention of vitamin D supplementation (mean fluorescence 311266.63). In the latter group there is a marked increase in the level of KLOTHO protein expression in the retinal layers. We also observed that the expression of the KLOTHO protein is the lowest in the group of diabetic mice, and early vitamin D supplementation increased the level of KLOTHO to its level in the control group but these results were not statistically significant.

Conclusions: We believe that the decrease in KLOTHO protein expression plays a role in the development of diabetic retinopathy in the mice retina. Late administration of vitamin D increases the expression of KLOTHO in the retinal tissue and might be a protective factor against the development of retinopathy. Future research is needed to determine the relationship between retinal KLOTHO levels and the clinical manifestations of diabetic retinopathy in mice.

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Testing elastic deformations on optical coherence tomography images of diabetic macular edema for data augmentation in deep-learning algorithms

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Purpose: A major challenge to the development of deep learning-based analysis of medical images is the need for large training datasets. Strategies to overcome the limited availability of annotated images include data augmentation, which provides an effective approach to artificially expand and diversify an existing dataset by applying transformations on original images. One such technique involves the introduction of random elastic deformations. To date, the most appropriate application of elastic deformation on retinal optical coherence tomography (OCT) images for training data has not been determined.
We explored this approach in the development of deep-learning model for automated detection of diabetic macular edema (DME) in OCT images.

Methods: Retinal OCT scans from patients with DME (n=320) were subject to elastic transformation, with the intensity of the deformation represented by an arbitrary value (σ). Sets of images, each comprising 100 pairs of scans (100 original & 100 modified), were grouped according to the intensity of the applied deformation, including low-, medium- and high-degree of augmentation (LDA, MDA, and HDA; (σ) range [1-6], [7-12], and [13-18], respectively). A fourth set of images, including 20 pairs of images subject to extremely high augmentation (σ [19-24]), served as control. Three retina specialists evaluated all datasets in a blinded manner, with images from each category randomly presented. Each grader was asked to rate each image as “original” versus “modified”. For each dataset, the rate of non-recognition of modified images, namely the assignment of ‘original’ value to modified images, was determined for each grader. **Results** Among the 3 graders, the rates of labelling modified images as ‘original’ ranged between (71-77%) for LDA, (63-76%) for MDA, and (50-75%) for HDA. In comparison, the corresponding rates of correctly identifying original images as ‘original’ ranged between (75-85%, $p>0.05$) for LDA, (73-85%, $p>0.05$ for graders 1 & 2, $p=0.01$ for grader 3) for MDA, and (81-91%, $p<0.005$) for HDA. In the control set, the rates of labelling modified images as ‘original’ were 20-65%.

Conclusions: Deformation of low-medium intensity (f 1-13) may be applied without compromising OCT image representativeness in the case of DME. Higher levels of deformation may result in a lower value as realistic examples. This may guide further design of training datasets for deep-learning models of automated retinal OCT image analysis.

Trace elements in cataracts of healthy and diabetic mice, and the effect of severe ocular ischemia

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Purpose: To examine the differences of elemental composition in lenses and retinae of wild type and diabetic mice, and the effect of optic nerve transection.

Methods: Lenses and retinae were harvested from wild type and diabetic mice (db/db) one hour following optic nerve transection (n=5 each). Another group of diabetic mice without optic nerve damage (n=14) served as control. The left eye also served as internal control. All diabetic mice were weighed, and glucose levels were checked to be >250 mg/dL.

Lenses ad retinae were analyzed by Particle Induced X-ray Emission (PIXE) for Ca, Cl, Na, K, Cu, Zn, Al, Fe and additional trace elements.

Results: The elemental composition of the mouse lens and retina differs significantly. Following optic nerve transection, lens Na to Cl ratio increased as compared to control as well as increased Ca levels. Retina from diabetic mice demonstrate increased Zn and Fe levels.

Conclusions: PIXE provides a unique tool for elemental composition analysis. It can be applied for small samples, such as mice ocular structures. Our study shows that similar to previous reports in rabbits by Ciaralli et al, using flame and graphite furnace atomic absorption spectrometry technique, the Na and Ca increase, Zn tend to increase, while K decreased. This may contribute to impaired permeability of the lens capsule. Mouse lenses and retinae have unique elemental compositions, but our findings are in line with Lekki et al who measured human lenses and reported elevated Zn in in senile cataract of diabetic subjects, also evaluated by PIXE analysis. We found Zn elevation in several of the lenses, and these findings were also detected in the retina of the same mice. Zn was found only in diabetic mice but not in the wild type group, following optic nerve transection. Fe was elevated only in the human diabetic reports, and not detected in the diabetic mice of this study.

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Neuro-ophthalmology
VOD

The prognostic value of OCT characteristics in compressive optic neuropathy

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Anterior visual pathway meningiomas represent 10% of all primary brain tumors.Most anterior visual pathway meningiomas (AVPM) are benign and slow-growing, but these tumors may affect visual functions, including visual acuity(VA) and visual field(VF).The prognostic value of macular ganglion cell complex count(GCC) quantification and its related parameters were not assessed in literature so far.

Purpose-To evaluate if OCT parameters (RNFL and GCC) have a prognostic value for visual outcomes in anterior pathway meningiomas.

Methods-We retrospectively reviewed the medical records of all patients with AVPM diagnosis,who were treated in Sheba medical center between 2011-2020. Included were patients with valid data containing pre intervention OCT exam in the CIRRUS® device and a minimum of 6 months follow up.Data on ophthalmic examinations and OCT parameters of the affected eye were retrieved-pre intervention(surgery or radiotherapy),6 months,1 year and 2 years post intervention .Data from post intervention periods was compared to the data in the pre intervention period.Spearman's correlation test was used to measure the strength of the association between clinical visual outcome in the different time periods and the pre interventional OCT parameters.

Results-186 patient's medical records were analyzed. 68 patients were excluded due to no treatment, 80 were excluded due to lack of data. 38 patients who met inclusion criteria were included in the study (28 female). The mean age at diagnosis was 52.8±12.2 years. Twenty four patients underwent surgery, 11 underwent radiotherapy and 3 both.Higher pre interventional average GCC was associated with better visual acuity at six months, one year and two years post intervention ($P \leq 0.04$, 0.005 and 0.028 respectively). Also, there was a significant correlation between visual field mean deviation (MD) and pre interventional GCC two years post intervention ($P \leq 0.001$). Average pre interventional RNFL thickness correlated with better visual acuity outcome in all time periods examined-($P \leq 0.038$,0.031 and 0.018 respectively).

Conclusions-Our results show that pre intervention OCT parameters , RNFL and GCC have a prognostic value in patients with anterior visual pathway meningiomas. To the best of our knowledge, although only 38 patients were included, this is the largest study examining the use of OCT as a prognostic factor for visual outcomes and the first regarding GCC.

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Retina
Live+VOD

Incomplete Blue Cone Monochromatism Phenotype Caused by Specific Exon 3 Haplotypes in the Red and Green Cone Opsins Genes Cluster

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Purpose: Blue cone monochromatism (BCM) is an X-linked retinopathy caused by mutations in the red and green cone opsins genes cluster. The aim of this study was to establish the clinical, genetic and electrophysiological characteristics of a specific form of BCM that we suggest to designate as incomplete BCM (iBCM).

Methods: In this retrospective study clinical and genetic data of patients harboring mutations in the OPN1LW/OPN1MW was analyzed. This included personal and familial history, best-corrected visual acuity (BCVA), refraction, a full clinical ocular examination, color vision testing, full-field electroretinography (ffERG), color fundus photographs, spectral domain optical coherence tomography (SD-OCT), and short-wavelength fundus autofluorescence (SWAF) imaging. Genetic analysis was performed using whole exome sequencing and Sanger sequencing. IBM SPSS Statistics v. 21.0 was used for data analysis.

Results: We identified 24 patients (14 families) harboring a combination of various haplotypes in exon 3 of the red and green cone opsins who presented with a milder incomplete phenotype of BCM as compared to a control group of 21 patients (from 3 families) with typical BCM. BCVA was significantly better in the iBCM group with a mean LogMAR of 0.43 ± 0.76 as compared with a LogMAR of 0.85 ± 0.72 in the typical BCM group ($p<0.0001$). The iBCM patients were more myopic, with a mean spherical equivalent (SE) of -7.81 ± 5.81 D [range (-9.875) – (-15.75); n=21], compared to the BCM patients -4.78 ± 5.27 D [range 0.25 – (-18.0)]; $p=0.0222$). The milder phenotype of iBCM patients was also reflected in the ffERG responses, with 30 Hz cone flicker responses being clearly measurable and significantly higher in the iBCM group (28.60 ± 15.02 μv (n=24)) versus practically non-detectable responses in BCM patients (0.66 ± 2.12 μv (n=21)); $p<0.0001$). Color vision testing using the D-15 Desaturated HUE test was available for 10/24 patients and was variable for the iBCM group, with tendency to show Dueteranopic-Protanopic axes of confusion. ffERG rod responses, fundus and ocular imaging features did not differ between the groups..

Conclusions: iBCM patients demonstrate higher myopia but better BCVA and significantly better ffERG cone flicker (30Hz) responses as compared to typical BCM patients. The phenotype is likely to be caused by partial aberrant splicing due to specific exon 3 haplotypes.

* Equally contributed

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Cornea
VOD

Automatic Image Processing in Histologic Slides of Conjunctiva With and Without Ocular Surface Squamous Neoplasia (OSSN)

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Purpose: OSSN is a spectrum of neoplastic diseases originating from conjunctival- and corneal- epithelium. Diagnosis (though made according to AJCC-TNM classification) is still somewhat subjective, depending on pathologistג€™s experience. Histopathologic findings implying OSSN include cellular features (e.g. atypia, high nucleus-to-cytoplasm, etc.) and tissue-related features (low inter-nuclei distances, maturation loss and more).

QuPath® is a software for automated bioimage analysis of histopathologic sections.
This study evaluates QuPath®'s potential role in differentiating normal conjunctivas from OSSN.

Methods: A retrospective cohort study, which included patients who underwent conjunctival excisional biopsy in our department, between 2016 – 2018. All slides were scanned and then annotated manually. Each annotation was diagnosed by a single pathologist (D.K.). Cellular and tissue features were measured for each annotation (nuclear morphometric features such as: area, diameter, circularity, eccentricity, nuclear dyes etc. and tissue architecture features, such as: nuclear density, nucleus-to-nucleus distance, number of “neighbors”, area of triangles (based on Delaunay Triangulation) etc.). “Kaggle” artificial intelligence feature was used to estimate differentiation ability between normal epithelium and OSSN using different cellular and tissue parameters.

Results: 150 annotations were recognized: 47 “normal epithelium”/squamous metaplasia, 49 on the OSSN spectrum, 50 subepithelial and 1 undiagnosed. Comparing normal and OSSN, four nuclear morphometric features showed statistically significant difference – minimal caliper, maximal caliper, perimeter and area. Three hematoxylin-optical-density (OD) parameters were significantly different – sum, minimum and mean. One parameter of eosin-OD differed significantly – OD sum. All tissue characteristics showed a significant difference (nuclear number and area, Delaunay triangular surface, inter-nuclear distance, number of neighbors, etc.).

Conclusion: QuPath® is a promising tool which can be utilized to help the pathologist in making a diagnosis. OSSN was significantly different from normal epithelium in several parameters. The parameters order of significance was found to be: tissue organization characteristics, nuclear morphometry, and nuclear staining (Hematoxylin > Eosin).

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Retina
VOD

Comparing the safety and performance of DTL fiber electrodes to Henkes type monopolar contact electrodes in clinical electroretinographic testing

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Background: Full-field Electroretinographic (ERG) testing is a widely used diagnostic tool for evaluation of the functional integrity of the retina, by recording and measuring the electrical potential produced by the retina in response to light stimulation under different conditions. The standard full-field ERG test is non-invasive, with the recording electrodes positioned on the anterior surface of the eye. In general, there are two main types of ERG electrodes:
1. Electrodes directly contacting and positioned on the cornea. Examples : monopolar Henkes-type electrodes.
2. Electrodes that establish electrical contact via the conjunctiva: example DTL fiber electrode that is fitted in the lower cul de sac of the conjunctiva.

Purpose: The aim of the study is to compare the clinical and electrical performance of a corneal contact lens ERG electrode (Henkes type) and the DTL microfiber ERG electrode in full field electroretinographic recording in normal subjects.

Methods: ERG testing was performed to obtaining isolated rod, combined rod-cone responses and oscillatory potentials in the dark-adapted state, followed by recording of single flash and flicker cone responses in the light-adapted state.

Results: Both types of electrodes showed similar wave response morphologies. Responses recorded with DTL fiber electrodes showed a statistically significant difference from those recorded using Henkes contact electrodes in the following parameters:

1. Amplitudes were significantly lower with DTL electrodes under eight stimulus conditions,
2. Implicit times were significantly shorter using the DTL electrodes under the isolated rod, dark-adapted standard flash combined a-wave and bright flash combined a-wave conditions. Amplitudes and implicit times of all other parameters and under other stimulus conditions did not significantly differ between DTL and Henkes electrodes.

Conclusions: We found that under certain stimulus conditions and with regard to specific ERG wave parameters DTL electrodes showed reduced amplitudes as compared to Henkes electrodes (i.e., affected the dynamic range), but visual acuity following testing, conjunctival and corneal condition as well as subjective patient experience were much better following testing with DTL fiber electrodes. These advantages may support conversion from contact lens electrodes to fiber electrodes in routine ERG testing.

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Cataract
VOD

Comparison of ocular parameters in cataract surgery candidates using different biometric devices

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Purpose: Precise biometric measurements before cataract surgery are crucial for successful intraocular lens (IOL) calculation. We compared pre-cataract surgery measurements obtained using Heidelberg's new Anterion, the IOLMaster 700 (Zeiss), and the Pentacam (Oculus).

Methods: Biometric measurements were taken with the IOLMaster700 and the Anterion, as well as corneal topography with the Pentacam. Values were compared for measurements of axial length (AL), anterior chamber depth (ACD), steep and flat K, cylinder and axis. Statistical analysis was performed using paired sample t-tests, Friedman test, Pearson's coefficient, and Cohen's d effect size. Clinical implications were derived from the IOL calculations for each device using the Barrett calculator.

Results: We compared measurements of 42 eyes (21 subjects; 38% female, mean age 65.2±14.9 years). Of these, 24 eyes also had corneal parameters measured with the Pentacam. Mean AL was 23.62±1.26 mm with the IOLMaster and 23.58±1.31 mm with the Anterion (P=0.004; Cohen's d 0.02). Mean ACD was 3.29±0.72 mm with the IOLMaster and 3.44±0.79 mm with the Anterion (P=0.04, Cohen's d 0.12). There were no statistically significant differences in the steep or flat K values between the three devices. The strongest correlations were observed between the Anterion and the Pentacam in the steep and flat K values (r=0.96 and 0.97, respectively; p<0.001). The weakest correlations were observed in the axis of the flat K between the IOLMaster and Anterion (r=0.45; p=0.003) and between the Anterion and Pentacam (r=0.42; p=0.02). When calculating the IOL using the Barrett calculator and mean values of the biometric devices, the Anterion values yielded a lower cylinder power by 0.75D.

Conclusions: Our results indicate excellent inter-device measurement agreement between the IOLMaster700 and the Anterion, rendering the two devices nearly interchangeable, with strong correlations also to the Pentacam corneal topography measurements. A clinically significant difference was observed only in the cylinder power of the calculated IOL.

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Anterior segment
Live+VOD

The potential role of tears in preventing ocular SARS-CoV-2 infection

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Purpose:

The main mode of SARS-CoV-2 transmission is via the respiratory route. SARS-CoV-2 receptors have been shown to be expressed on the ocular surface, which would suggest that the eye could also be a site for SARS-CoV-2 infection and transmission. Surprisingly, while a few studies did report that exposure of unprotected eyes to the virus could lead to infection, this seems to be a rare occurrence. We speculated that tears might have a protective role against SARS-CoV-2 infection. In the present study, we examined the anti-SARS-CoV-2 activity of human tears.

Methods: Basal tear fluid was collected from the lower lid margin and inferior fornix of healthy individuals who were seronegative for SARS-CoV-2, using a 20-microliter micropipette fitted with a sterile blunt tip. In the first part of the study, we employed pooling of tears (combined from different subjects) to increase the total volume of collected tears. Next, in order to examine possible differences between individuals, larger volumes of tears were collected from each subject, and tested separately. Tears were subjected to antiviral assay in VERO-E6 cells, with combined monitoring of the viral cytopathic effect and viral RNA levels, using qRT-PCR.

Results: A first tears-pool, combined from 7 healthy individuals, exerted significant inhibition of SARS-CoV-2 infection. An additional unrelated tears-pool, combined form 30 (different) healthy subjects, did not show significant viral inhibition. Hypothesizing that potential variability of tear-composition between individuals may underlie the differences in the antiviral effect, we next tested the antiviral activity of tears obtained separately from 8 independent individuals. Tear samples from three of these subjects demonstrated significant anti- SARS-CoV-2 activity, three tear samples showed moderate inhibition, and two tear samples did not exhibit any antiviral activity.

Conclusions: Our results demonstrate that human tears could suppress SARS-CoV-2 infection, and further suggest that there is variability of this antiviral effect between individuals. Further studies are needed to specifically identify the active anti-SARS-CoV-2 component/s within tears and uncover their mode of action.

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Cornea
VOD

Belantamab Mafodotin Induced Keratopathy: a 2 cases and review of literature

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Purpose: To report two cases of Belantamab Mafodotin Induced Keratopathy, to share our experience and raise awareness of corneal side effects of a newly developed experimental drug.

Methods: The data in the current cases were obtained from the Emek Medical Center records. A literature search was performed and included a systematic review utilizing the PUBMED databases based on the combination of search terms: “Belantamab and keratopathy” OR “Belantamab induced microcystic epithelial changes”.
Case #1: A 78-year-old male patient diagnosed with refractory Multiple Myeloma (MM) since 2014 who had progressive disease following 4 prior lines of anti-myeloma therapy. He had undergone cataract surgery in both eyes. On ophthalmologic follow-up after 2 cycles of 2.5 mg\kg Belantamab, presented with loss of visual acuity and discomfort. Ophthalmologic examination revealed bilateral central corneal microcystic epithelial changes (MEC) on slit lamp microscopy and punctate staining with fluorescein (that were not present at initial screening). Best corrected visual acuity (BCVA) was OD 6/7.5 OS 6\9 (same as baseline). After the fourth cycle, increased number of MECs were noted OU and BCVA was OD 6/10 OS 6/12. Therefore, the next infusion was postponed by 3 weeks and he was instructed to use preservative-free lubricant eye drops OU. On follow-up one month later, slit lamp examination showed improvement of the findings.
Case #2: a 60-year-old female patient diagnosed with MM since 2014, who had also progressive disease, following 4 lines of anti-myeloma therapy. She had a history of blepharitis OU, returned for ophthalmologic follow-up after the first cycle of 2.5 mg\kg Belantamab, she had no ophthalmic complaints, on examination: reduced visual acuity with BCVA OU 6/9 (on screening: OS 6/7.5 OD 6/9-2) and on slit lamp microscopy bilateral peripheral corneal MEC. Therefore, Belantamab dose was reduced by 25%. On the next follow-up there was no further deterioration of the visual acuity.

Results: here we describe two cases of bilateral corneal microcystic epithelial changes after treatment with Belantamab for refractory MM, the first and the second cases were grade 3 and 2 on KVA scale (respectively), leading to withholding treatment in the first case and reducing the dose by 25%. On follow-up both cases had no deterioration.

On literature review there are limited available reports, with the PHASE II (DREAMM-II study) being the main resource of the data available, showing that 71% of patients received Belantamab had keratopathy (44% grade 3-4), 53% had changes in visual acuity (28% grade 3-4), 22% had blurred vision (4% grade 3-4) and 4% had dry eyes. Most keratopathy events developed within the first 2 treatment cycles, For patients in whom events resolved, the median time to resolution was 2 months (range: 11 days to 8.3 months).

Conclusion: Belantamab was found to have favorable anti-myeloma activity in patients with relapsed refractory MM, who otherwise have almost no other treatment options. Therefore, close ophthalmologic follow-up and early identification and management of Belantamab induced keratopathy are crucial. Further research is required in order to develop new treatment strategies to lower or even prevent ocular adverse effects of Belantamab.

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Oncology
VOD

Survival of uveal melanoma patients with additional malignancies.

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Purpose: Patients with uveal melanoma (UM) may also develop other tumors before or after being diagnosed with UM, but there is little characterizing data in the literature. We assessed the survival of UM patients with second malignancies in Israel.

Methods: A retrospective review and analysis of a cohort of 927 uveal melanoma patients at the Ocular Oncology Service of the Hadassah University Hospital from 1982 to 2017.

Results: Seventy-four (7.9%) patients (42 (57.5%) women) had second tumors. In 37 (50.7%) patients UM was diagnosed 69.5 months before a second malignancy, while in the rest it appeared 128.3 months after another malignancy. The most common malignancies in descending order were: breast (32%), colon (16%), renal cell carcinoma (9%), cutaneous melanoma (8%), basal or squamous cell carcinoma (8%), and other tumors (27%). The mean (±SE) survival for UM patients without and with second malignancies was similar (230.4 (±7.5) vs. 200.9 (±16.9) months, respectively, Log-Rank p=0.48). Survival was also similar whether UM was diagnosed first or after another malignancy (205.5 (±19.6) vs. 159.1 (±16.8) months, respectively, Log-Rank p=0.52). There is a trend for a higher chance to develop UM metastases if patients did not have a second malignancy (16.7% vs. 9.5%, respectively, Likelihood ratio p=0.083). Whether UM was diagnosed first did not impact that chance (Likelihood ratio p=0.50).

Conclusions: Second malignancies in UM patients are uncommon and do not affect the overall survival.

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Oncology
VOD

Ocular Side Effect of Novel Biological Therapies

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Purpose: To examine the ocular side effects of anti-cancer biological therapies.

Design: Retrospective cohort study.
Participants: All patients with ocular side effects while receiving biological anti-cancer treatment from January 2012 to December 2017.

Methods: All medical records were retrospectively reviewed for demographics, primary malignancy, metastasis, type of treatment (mechanisms of action), laterality, ocular side effects, ophthalmic treatment, ocular and systemic disease prognoses. Division by mechanisms of action and a comparison of groups was done.

Results: A total of 22 patients were found. Nineteen patients (86.36%) had metastatic disease and 3 patients (13.64%) had stage 3 cancer disease. The treatment groups were: 8(36.4%) BRAF, 4(18.2%) Programmed Death Ligand-1, 2(9.1%) Mitogen-activated protein kinase1/2, 2(9.1%) Anaplastic Lymphoma Kinase, 1(4.5%) Cytotoxic T-Lymphocyte Antigen-4 and 1(4.5%) Epidermal Growth Factor Receptor.

Eighteen patients (81.8%) had bilateral ocular side effects. The most common ocular side effect was uveitis (40.9%) followed by dry eye (22.7%) and Central serous retinopathy (22.7%). One patient (4.5%) presented with Central retinal artery occlusion and one (4.5%) with Branch retinal vein occlusion. All patients were treated according to their ocular side effect.
At the end of follow up the ocular disease resolved in (27.27%) were stable in (59.09%) and progressed in (3.63%). 18 patients (81.8%) were alive at the end of the study.

Conclusion: Biological anti-cancer therapies can cause ocular discomfort, ocular morbidity and vision loss. Patients sold be screened for ocular side effects, since early identification of the ocular side effects may lead to better visual prognosis.