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

PROGRAM & ABSTRACTS
44th Annual Meeting

Sammy Ofer Hall, Tel Aviv Sourasky Medical Center

July 11th , 2024

תכנית ותקצירים
הכינוס השנתי ה-44

אולם סמי עופר, בנין הלב

המרכז הרפואי תל-אביב ע"ש סוראסקי

11 ביולי, 2024

עריכת התוכנית: דר' סאמר חטיב, דר' שירי סודרי, דר' אביגיל בריוזקין, דר' הדס בן אלי, פרופ' רובי פוירשטיין

הפקת הכינוס ועיצוב והבאה לדפוס:

דבורה מרקס אוחנה, פרופ' דינה צור, פרופ' שחר פרנקל

תודה לחברות החסות

ISRAELI SOCIETY FOR VISION AND EYE RESEARCH The 44th Annual Meeting, July 11th 2024 Program at a glance	
Session	**Time**
Gathering and Coffee	08:00
Opening remarks	08:30
Cornea, external eye disease and refraction Moderators: Avi Solomon & Hadas Ben-Eli	08:35
Glaucoma, Neuro-ophthalmology and Visual neuroscience Moderators: Nitza Goldenberg-Cohen & Alon Zahavi	09:40
Coffee break	10:40
Retina Moderators: Libe Gradstein & Dinah Zur	11:00
Oculoplastics Moderators: Ofira Zloto & Oded Ohana	11:20
Lunch break	13:00
General meeting Awards, updates & election results	13:50
Guest Lecture - **Dr. Vered Gigi** From a vision to a vibrant business – creating company – why helping patients is not enough	14:00
Animal and Cell models Moderators: Dror Sharon & Shiri Soudry	14:30
Genetics & Retinal degeneration Moderators: Tamar Ben-Yosef & Eran Pras	15:55
Cataract and Uveitis Moderators: Arie Marcovich & Liat Gantz	17:10
Closing remarks	17:35

יושבי ויושבות הראש של האגודה הישראלית לחקר העין והראייה

CHAIRPEOPLE OF THE ISRAEL SOCIETY FOR VISION AND EYE RESEARCH

Prof. Elaine Berman	1979 -1982	פרופ' איליין ברמן ז"ל
Prof. Michael Belkin	1983-1985	פרופ' מיכאל בלקין
Prof. Saul Merin	1986-1989	פרופ' שאול מרין ז"ל
Prof. Shabtay Dikstein	1990-1993	פרופ' שבתאי דיקשטיין
Prof. Fabian Abraham	1994-1996	פרופ' פביאן אברהם ז"ל
Prof. Ido Perlman	1997-1999	פרופ' אידו פרלמן
Prof. Jacob Pe'er	2000-2003	פרופ' יעקב פאר
Prof. Ahuva Dovrat	2004-2006	פרופ' אהובה דברת ז"ל
Prof. Mordechai Rosner	2007-2009	פרופ' מרדכי רוזנר
Prof. Eyal Banin	2010-2012	פרופ' איל בנין
Prof. Avi Solomon	2012-2015	פרופ' אבי סלומון
Prof. Dror Sharon	2015-2018	פרופ' דרור שרון
Prof. Itay Chowers	2019-2021	פרופ' איתי חוברס
Prof. Shahar Frenkel	2021-2024	פרופ' שחר פרנקל

חברי וחברות ועד האגודה הישראלית לחקר העין והראייה
BOARD MEMBERS OF THE ISRAEL SOCIETY FOR VISION AND EYE RESEARCH

Prof. Shahar Frenkel – Chairman	**פרופ' שחר פרנקל- יו"ר**
Prof. Jaime Levy – Treasurer	**פרופ' חיים לוי - מזכיר-גזבר**
Prof. Dinah Zur	**פרופ' דינה צור**
Dr. Samer Khateb	**דר' סאמר חטיב**
Dr. Shiri Soudry	**דר' שירי סודרי**
Dr. Avigail Beryozkin-Muniz	**דר' אביגיל בריוזקין-מוניץ**
Dr. Hadas Ben-Eli	**דר' הדס בן-אלי**
Prof. Ruby Shalom-Feuerstein	**פרופ' רובי שלום-פוירשטיין**

Awards

מלגות נסיעה ל- ARVO למרצות של העבודות המצטיינות 2023 ניתנות בעזרת מענקים שנתרמו באדיבות **עמותת "לראות".**

1st prize

Chen Matsevich

Division of Ophthalmology, Hadassah Medical Center, Faculty of Medicine, The Hebrew University of Jerusalem, Jerusalem, Israel

Gene Augmentation Therapy Attenuates Retinal Degeneration in a Knock-Out Mouse Model of Fam161a Retinitis Pigmentosa

2nd prize

Shlomit Jaskoll

Department of Ophthalmology, Hadassah-Hebrew University Medical Center, Jerusalem, Israe

Sodium Iodate Induced Retinal Degeneration in BALB/C Mice

3rd prize

Shalini Dimri-Wagh

Department of Genetics and Developmental Biology, The Rappaport Faculty of Medicine and Research, Technion-Israel Institute of Technology

Reprogramming to rescue total stem cell loss

80% ממקרי העיוורון ניתנים למניעה באיתור מוקדם וטיפול מתאים

עמותת "לראות", הוקמה ב-2006 במטרה למצוא מרפא למחלות עיניים הגורמות לעיוורון ולהקטין את מספר החולים. העמותה פועלת להעלאת המודעות לחשיבותן של בדיקות ראייה סדירות, למניעת התפתחות מחלות עיניים ואיתור פגמים בנוסף, עד היום אנו מעורבים ב- 21 מחקרים רפואיים בתחום הראייה.

בעלי תפקידים בעמותת לראות

נשיא העמותה	**יו"ר העמותה**	**מנכ"ל העמותה**
פרופ' מרדכי שני	**אוהד להב**	**נדין הולנדר**

חברי הועד המנהל:

פרופ' דרור שרון: יו"ר המועצה המדעית,

אוהד להב ,פרופ' מרדכי שני, פרופ' איתי חוברס, , פרופ' אריה סולומון, פרופ' אירית בכר , פרופ' אדו פרלמן,פרופ' ענת לוינשטיין, פרופ' חנא גרזוזי, פרופ' יעקב פאר, פרופ' אהוד אסיה, פרופ' דרור שרון, פרופ' יאיר מורד, , פרופ' חני ורבין, ד"ר רונית לוינגר, מר מרק עמוס, ד"ר ניר ארדינסט, פרופ' שחר פרנקל, פרופ' גאי קלינמן, פרופ' אלעד מיוסד בפרופ' תמר בין יוסף.

הפרויקטים של עמותת לראות

בדיקות בקהילה

קשישים

עשרות אלפי קשישים בישראל, מקבלים את הידרדרות ראייתם, לעיתים עד לכדי עיוורון, כגזירת גורל. הם לא מודעים לכך שהרפואה השתכללה והתקדמה כך שניתן במקרים רבים להציל ולשפר משמעותית את ראייתם ואת איכות חייהם.

לשם כך, החלטנו בעמותת לראות להביא את המרפאה לסביבתם הקרובה של הקשישים - למועדון, למרכזי יום ומתנסים, שם אנו עורכים ימי בדיקות מרוכזים הפרויקט מתקיים בכל הארץ.

מאז מגפת הקורונה עמותת לראות מקיימת שירות של ביקורי בית של רופא עיניים ו/או אופטומטריסט למרותקים לביתם.

ילדים

קוצר ראייה ועין עצלה הן שתי בעיות העיניים נפוצות בקרב ילדים. בשיתוף עם גני ילדים ורשויות מקומיות אנו עורכים בדיקות עיניים לילדים החל מגיל פעוטות ועד גילאי בית ספר.

הנגשת מידע ויעוץ רפואי

עמותת לראות מחויבת להעלאת מודעות לבריאות העין ומניעת עיוורון.

העמותה מעמידה לרשות הציבור הרחב פורומים מקצועיים אונליין בהובלת רופאים בכירים בנושאים שונים כמו: אובאיטיס, גלאוקומה, סכרת, קטרקט ועוד.

קידום המחקר למניעת עיוורון:

השנה יצא קול קורא למחקרים בסכום של 200.000 שקל בניהול המועצה המדעית .

גם מקדמים פרויקט להעלאת מודעות למניעת עיוורון בדור השני בניהול פרופ' טוביה חורב.

המטה הישראלי למחקר חדשני בתאי גזע

כחלק ממאמץ לאומי עמותת לראות מובילה את הקמתו של המטה הישראלי למחקר בתאי גזע אשר ישמש כגוף המאגד תחתיו חוקרים מכל התחומים ויוביל מחקר חדשני בתאי גזע.

חודש המודעות:

מדי שנה בחודש דצמבר העמותה יוצאת בקמפיין ארצי להעלאת מודעות לבעיות שונות הקשורות בראייה ועיוורון. פעילויות חודש המודעות מתקיימות הרצאות, חשיפה במדיה, הפקת מגזין בנושא קידום בריאות העין בשיתוף איגוד רופאי העיניים בהוצאת עיתון 'הארץ' .

השנה בנושא אופתלמולוגיה ו-AI בניהול פרופ' אירית בכר.

פעילות בזמן המלחמה:

בדיקות עיניים למפונים בבתי מלון בכל הארץ וקניית משקפי מגן מיוחדים לחיילים לוחמים שהציל לא מעט עיניים בקרב.

בקרו אותנו באתר: https://www.eyes.org.il/Home, להרשמה לניוזלטר:

https://www.eyes.org.il/%D7%A6%D7%95%D7%A8-%D7%A7%D7%A9%D7%A8

WWW.EYES.ORG.IL

NADINE@EYES.ORG.IL

Guest speaker

Thursday, July 11th, 2024, at 14:00

The Sammy Ofer Conference Hall, Tel-Aviv Sourasky Medical Center (Ichilov Hospital)

Dr. Vered Gigi

From a vision to a vibrant business
Creating a company - why helping patients is not enough

Vered Gigi is a Principal with aMoon Velocity, where she drives due diligence on early-stage companies, with a focus on pharmaceutical and medical device companies.
Prior to joining aMoon, Vered served as Chief Scientific Officer at Cure Pharmaceutical, a drug delivery company in the pharmaceutical & wellness space, and before that as a project leader at BCG Management Consulting in their healthcare practice. Her experience spans strategy, business development, R&D, and operations in both corporate and startup settings.
Vered's passion is in translating exciting science into therapies in a practical and sustainable fashion. Her experience taught her that not all discoveries are made equal and there is a time and a place for each.
Vered completed her PhD in Immunology at the University of Pennsylvania, where she investigated nucleases and DNA repair mechanisms in the immune system and their contribution to cancer. She holds a BSc and MSc in Biomedical Sciences from Tel Aviv University.

		שעת התחלה	מציגים	#	כותרת
התכנסות, הרשמה, קפה		08:00			
ברכות ופתיחה		08:30			פרופ' שחר פרנקל
קרנית, עין חיצונית ורפרקציה	עדכוני בזק	08:35	רעות יפרח	C1	Complications and compliance in professionally-managed and self-directed contact lenses compared with noncontact lens wearers
		08:37	ליאת גנץ	C2	Automatic vs. Manual Methods of Assessment of the Visible Iris Diameter
		08:39	מרגריטה ספיר	C3	Atopic Disease and Astigmatism: A Population-Based Study
		08:41	יונתן לוין	C4	Refractive Error Progression Over Twelve Months in Israeli Boys Across Different Religious Backgrounds.
		08:43	אור שמואלי	C5	Refractive Predictive Errors Using Barrett II, Hoffer-Q, and SRKT Formulae For Pediatric IOL Implantation
		08:45			
		08:47	דין ליכטר	C7	Clinical And Epidemiological Factors Affecting Donor Corneal Endothelial Cell Count
	דיווחים מלאים	08:50	מתן ארזי	C8	First-in-human Clinical Trial of a Novel Eyelid warming Device in Meibomian Gland Dysfunction
		08:55	איתן לבני	C9	Possible correletion between chemotherapy treatment of corneal donors to lower endothelial cell quality of their grafts
		09:00	אנה בונין	C10	accelerated CXL versus accelerated contact lens–assisted CXL for progressive keratoconus in adults
		09:05	אורן פאר	C11	Fire ant punctate keratopathy in companion animals. 100 canine and feline cases
		09:10	סטפן ריצ'רד	C12	Teprotumumab As a Potential Therapy For Human Pterygium
		09:15	עדן אמיר	C13	Factors Influencing Consent for Corneal Donation: Insights from a Prospective Study
		09:20	מוחמד גארא	C14	Prevalence and Risk Factors of Keratoconus in Israeli Arabs
		09:25			דיון פרופ' אבי סולומון ודר' הדס בן-אלי
נוירואופתלמולוגיה, גלאוקמה ופיזיולוגיה של הראייה	עדכוני בזק	09:41	הדס בן ארי	N1	Changes in focal Rod-, Cone- and Melanopsin-mediated pupil light responses associated with Parkinson disease progression
		09:43	רביד דורון	N2	Comparative Study of Near Work Behaviors Among Ultra-Orthodox and Non-Orthodox Jewish Male College Students
		09:45	עמית לכטמן	N3	COLOR VISION TESTING – COMPARING ISHIHARA BOOKLET TO SMARTPHONE APPLICATIONS
		09:47	שני שפרלינג	N4	Adjusting for Reproducibility Limit Can Modify RNFL Thickness Color Coding
	דיווחים מלאים	09:50	אלון זהבי	N5	Elevated Iron Levels In Tears of Patients Diagnosed With WDR45 X-Linked Optic Atrophy
		09:55	ברייס וופו	N6	Role of Visual Evoked Potential and Ocular Trauma Score as Predictors of Visual Recovery in Eye Globe Injuries.
		10:00	עליזה גלר	N7	Comparison of inter and intra-rater reliability of the measurement anisocoria using optical coherence tomography and a smartphone camera
		10:05	רחל שמש	N8	Longitudinal optical coherence tomography indices in pediatric idiopathic intracranial hypertension
		10:10	גל אנטמן	N9	Analysis of the anatomical and functional ocular changes related to spaceflight
		10:15	ארי לשנו	N10	Use of Topographical Structure–Function Agreement For Glaucoma Screening
		10:20			דיון: פרופ' ניצה כהן, ד"ר אלון זהבי
הפסקת קפה		10:40			

Long-term impact of carotid endarterectomy on choroidal and choriocapillaris perfusion. The INFLATE study	R1	עומר טריביצקי	11:00	עדכוני בזק	רשתית
Vitreous and blood biomarkers associated with proliferative diabetic retinopathy	R2	ג'וואד מסאלחה	11:02		
Development and progression of geographic atrophy under anti-VEGF treatment in eyes with neovascular age macular degeneration: a quantitative fluid approach	R3	דואה מסארוה	11:04		
Electrophysiological based investigation of hypothermia effect on the feasibility of retinal resuscitation following ischemia.	R4	עדן בוזה	11:06		
The clinical characteristics and outcome of patients undergoing consecutive PPV with silicone oil for failed surgery for RD	R5	טירן גולני	11:08		
A seven-year electroretinography follow-up of a patient with melanoma-associated retinopathy stabilized on pembrolizumab treatment.	R6	מיכאל אוסטרובסקי	11:10		
Fabrication and characterization of 3D-printed, stem cell-derived tri-layered retinal implants	R7	מקסים בז	11:12	דיווחים מלאים	
Retinal Gene expression in response to Aβ results in a transcriptomic footprint similar to age-related macular degeneration	R8	שחף סיגל דרור	11:17		
The presence of subretinal drusenoid deposits as a predictor of cardiovascular disease	R9	נתן לישינסקי	11:22		
A Potential Role for Clusterin in the Pathogenesis of Age-Related Macular Degeneration (AMD)	R10	בתיה רינסקי	11:27		
The correlation of genetic risk scores with OCT biomarkers in AMD	R11	שלומית יסקול	11:32		
Choroidal vasculature segmentation using SOTA AI model.	R12	אורלי גלאור	11:37		
Switching Anti-VEGF Therapy in Neovascular Age-Related Macular Degeneration: New Insights on Efficacy Using Automated Volumetric Retinal Fluid Analysis	R13	דינה צור	11:42		
Dyslipidemia in Age-related Macular Degeneration	R14	עדי קרמר	11:47		
דיון: ד"ר ליבה גרדשטיין, פרופ' דינה צור			11:52		
Xanthelasma Palpebrarum is Not Associated with Dyslipidemia or Cardiovascular Disease: A Case Control Study	P1	יעל לוסטיג	12:10	עדכוני בזק	פלסטיקה
Punctal Atresia as a Clinical Indicator of Systemic Genetic Anomalies	P2	אור גיל	12:12		
Lacrimal Obstruction in Craniosynostosis: Anatomical and Genetic Risk Factors	P3	דפנה לנדאו	12:14		
Characterization Of The Ocular Microbiome In Anophthalmic Patients	P4	רז רובינשטיין	12:16	דיווחים מלאים	
Orbital Development in Children with Retinoblastoma: An Imaging-based Study	P5	לי נוסבאום	12:21		
A Novel Semi-Automated MRI-Based Method for Orbital Volume and Contour Analysis Compared with CT-Based Dimensions	P6	ליטל סמדר	12:26		
Nasal and temporal intraconal orbital fat densities differ on computerized tomographic scans of normal orbits	P7	עינב בהרב	12:31		
Computer Aided Diagnosis of Eyelid skin tumors Using Machine Learning	P8	אופירה זלוטו	12:36		
Should we ask AI for approval for blepharoplasty surgery?	P9	בר יעקובי	12:46		
דיון: פרופ' אופירה זלוטו, ד"ר עודד אוחנה					
			13:00		הפסקת צהריים
			13:50		עדכונים, בחירות
Vered Gigi PhD. *From a vision to a vibrant business - creating a compnay - why helping patients is not enough*			14:00		מרצה אורחת

The retinal pathways triggered by Amyloid-β42 30 days after exposure are related to AMD pathological processes.	M1	רוני בן צבי	14:30	עדכוני בזק	מודלים פרה קליניים וטיפולים חדשים
Ranibizumab clearance through the aqueous outflow pathway system in a rat model	M2	אסף בן ארצי	14:32		
A novel delivery device for scleral cross-linking for the treatment of myopia	M3	יגאל רוטנשטרייך	14:34		
Exosomes derived from mesenchymal stem cells attenuate Amyloid β toxicity in rat retina	M4	אמאנדא קרואני	14:37	דיווחים מלאים	
Light-dark transition test in wild type mice and animals with advanced retinal degeneration	M5	רותם מזרחי	14:42		
Cross-linked hyaluronic acid enhances tear film concentrations of topical antibiotics in canine eyes	M6	דקלה ארד	14:47		
Pathological Ultrastructural Alterations of Optic Nerve Axons in Cobalt Toxicity: Correlation with MRI Imaging Changes	M7	באסל עוביד	14:52		
The role of the CCR1 receptor during retinal degeneration	M8	שרה חיון	14:57		
in-vitro Differentiation and Further in-vivo Maturation of Retinal Precursor Cells Derived from Human Embryonic Stem Cells	M9	חן מצביץ	15:02		
Investigating the Bmp4 pathway regulation effect on Photoreceptors' neurite outgrowth in in-vitro and ex-vivo models	M10	אביעד סלוטקי	15:07		
Correction of the Achromatopsia-causing splice defect created by the deep intronic CNGB3- c.1663-1205G>A mutation using an antisense oligonucleotide	M11	ספיר שלום	15:12		
iPSC-derived RPE models for RP11 disease modeling and treatment development	M12	יפעת שר	15:17		
A new rat model for retinal degeneration: The GCaMP6f+\- RCS-\- Rat	M13	תמר אזרד ליבוביץ	15:22		
דיון: פרופ' דרור שרון, ד"ר שירי סודרי			15:27		
			15:40		הפסקת קפה

ADAR-based RNA editing and splice-region variants in ABCA4	G1	נינה שניידר	15:55	דיווחים מלאים	גנטיקה וניוון רשתית
A founder homozygous nonsense mutation in CREB3 causes a variable retinal dystrophy in three North-African Jewish families	G2	מנאר סלאמה	16:00		
The landscape of mutations causing inherited retinal diseases (IRDs) in the Israeli population	G3	דרור שרון	16:05		
Mutations in PRPF31 are associated with mitochondrial dysfunction in human RPE	G4	טל שאדי	16:10		
Using minigene-based splice assays to evaluate the pathogenicity of variants identified in patients with inherited retinal diseases	G5	סופיה איצקוב	16:15		
Clinical characterization of RP11 patients and asymptomatic carriers in Israel	G6	מריאן חיאדרי	16:20		
C19ORF44 is a novel gene which encodes a nuclear protein and is associated with autosomal recessive retinal dystrophy	G7	מעין מזרחי	16:25		
ADAR enzyme – mediated RNA editing as a therapeutic tool for choroideremia	G8	שלהבת יזרעאלי	16:30		
Disruption of common ocular developmental pathways in patient-derived optic vesicle models of microphthalmia	G9	יונתן אינטרכט	16:35		
Diverse Ancestry Analysis: The IAMDGC 2.0	G10	מישל גרונין	16:40		
A novel large deletion in chromosome X is associated with nystagmus in male and female members of an extended family	G11	אלעד בראב	16:45		
Autistic spectrum disorder and psychomotor delay in retinoblastoma patients	G12	שחר פרנקל	16:50		
דיון: ד"ר ערן פרס, פרופ' תמר בן יוסף			16:55		

The Influence of Age and Sex on Cataract Surgery Complications and Outcomes	U1	אילת גולדשטיין	17:10	בזק	קטרקט ואובאיטיס
Results of Cataract Surgery in Eyes with Adult-Onset Foveomacular-Vitelliform Dystrophy (AFVD)	U2	איתי ניצן	17:12	דיווחים מלאים	
Benchmark of cataract segmentation architecture for Artificial Intelligence	U3	אלון טיאוסנו	17:17		
4485-3p MicroRNA as biomarker for uveitis in juvenile idiopathic arthritis	U4	יעל שרון	17:22		
דיון: פרופ' אריה מרקוביץ, דר ליאת גנץ			17:25		
			17:35		סיכום

תקצירים

Abstracts

Cornea, external eye disease and refraction

Rapid fire – 2 minutes

C1
Reut Ifrah

Complications and compliance in professionally-managed and self-directed contact lenses compared with noncontact lens wearers

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Purpose: To test the impact of professional management of soft contact lens (CL) wear on symptoms and ocular complications.
Methods: Subjective symptoms and ocular complications of soft CL users who were not followed up (self-directed, SD), were compared to users who were prescribed CLs and their care professionally managed in optometry practices (PM), and to a control group of non-CL wearers. Habitual visual acuity, subjective dry-eye symptoms, and corneal abnormalities were assessed in all participants. CL wearers filled-out a usage habits questionnaire, and their CL fit was assessed. Outcomes were compared using Kruskal-Wallis and Chi Squared tests.
Results: The SD, PM, and non-CL wearers cohorts included 127 (mean age:24.3±5.1, median:23, range:16-45 years,104 female), 132 (mean age:25.5±6.2, median:23, range:18-43 years,103 female), and 56 (mean age:22.3±3.5, median:21, range:18-39 years,36 female) participants, respectively. Meibomian gland dysfunction grade ($p=0.004$, $p<0.0001$), limbal redness (both $p=0.04$), corneal neovascularization (both $p=0.003$), and papillary conjunctivitis ($p<0.0001$,$p=0.005$) were significantly worse in SD CL wearers compared with both the non-CL wearers and PM CL wearers, respectively. Conjunctival staining was significantly worse in the SD cohort compared with the PM cohort ($p=0.01$). 38.6% of the SD compared with 22.8% of the PM CL wearers, had an inappropriate refractive correction ($p=0.006$). SD CL wearers wore CLs significantly more years (mean and median 1 year,$p=0.008$), for more daily hours (mean and median of 2 hours,$p<0.00001$), and tended to nap or sleep with their CLs compared with the PM CL wearers (47 vs. 29,$p=0.02$). The cohorts did not differ in their subjective symptoms.
Conclusions: Complications are significantly more prevalent in SD CL wearers compared with PM CL wearers. SD CL wearers demonstrated a tendency to wear CLs with incorrect powers, and were less compliant with napping or sleeping with the CLs compared with PM CL wearers. These findings emphasize the importance of fitting, patient education and follow-ups in CL wearers.

Cornea, external eye disease and refraction

Rapid fire – 2 minutes

C2

Liat Gantz
Hadassah Academic College

Automatic vs. Manual Methods of Assessment of the Visible Iris Diameter

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Purpose: The horizontal visible iris diameter (HVID) extends from nasal to temporal limbus and is important in contact lens fitting and ocular surgeries. It can be assessed manually using a mm ruler, a designated HVID ruler, and viewing through the slit lamp biomicroscope; or automatically, using a topographer. This study examined the interchangeability of these four measurement methods.
Methods: The HVID of healthy participants was measured three consecutive times in the left eye and once in the right eye using four methods in a randomly determined order. The measurements of the four methods were compared using correlation and Bland-Altman tests, as well as a Friedman test with post-hoc analysis. Differences between methods that were greater than 1.00 mm were defined outside of the clinically acceptable limits.
Results: The HVID of 31 participants (87% female, mean age: 24±4, range: 21-38) was 11.42±0.62, 11.68±0.40,11.46±0.45, and 11.91±0.48 mm using the ruler, HVID, slit, and topographer, respectively. The methods were significantly different ($F(df=3,120)=17.09$, $p \leq 0.00$) with post-hoc tests demonstrating differences between all methods except slit vs. HVID and slit vs. ruler. The mean difference between each pair of tests ranged between 0.11-0.48 mm, with limits of agreement all greater than 1.00 mm.
Conclusions: The methods of assessment of HVID are not interchangeable. Automatic measurements were largest compared to manual measurements. Clinicians should use a consistent measurement method when assessing patients longitudinally.

Cornea, external eye disease and refraction

Rapid fire – 2 minutes

C3
AC
Margarita Safir
Shamir Medical Center (Assaf Harofeh)

Atopic Disease and Astigmatism: A Population-Based Study

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PURPOSE: To assess the relationship between atopic disease and astigmatism in adolescence and young adulthood.
METHODS: In this population-based cross-sectional study 897,811 medical records of Israeli adolescents and young adults without keratoconus were reviewed. The prevalence of low-to-moderate (3.00> D ≥0.75) and high (≥ 3.00 D) astigmatism were calculated in cases with and without atopic disease, including ocular atopic disease (OAD), asthma, allergic rhinitis, atopic dermatitis, angioedema/urticaria, and history of anaphylaxis. Relationships were analyzed using multinominal logistic regression, with adjustments for relevant sociodemographic factors.
RESULTS: A total of 897,811 adolescents were included in the analysis (mean age 17.2 ±0.8 years, 57.8% men). OAD was found in 4,702 individuals, with a prevalence of 0.5%. Adolescents with OAD demonstrated a gradual increase in odds ratio (OR) for low-to-moderate and for high astigmatism (OR 1.16, 95% CI 1.07–1.27 and OR 2.10, 95% CI 1.63–2.70, respectively). This group also showed increased OR for with-the-rule astigmatism (OR 1.34, 95% CI 1.21–1.48). Other atopic diseases were associated with more modest ORs for low-to-moderate (OR 1.09, 95% CI 1.07–1.11) and for high astigmatism (OR 1.10, 95% CI 1.02–1.19), persisting across all axis orientations. Sensitivity analysis revealed a dose-response relationship between OAD severity and astigmatism, and consistent point estimates in a group of 1,331 adolescents diagnosed with OAD during military service.
CONCLUSIONS: This study establishes an association between OAD and astigmatism, highlighting the importance of effective OAD management. Further research into tailored therapeutic interventions that address both conditions concurrently is needed.

Cornea, external eye disease and refraction
Rapid fire – 2 minutes

C4
Jonathan Levine
Hadassah Academic College

Refractive Error Progression Over Twelve Months in Israeli Boys Across Different Religious Backgrounds.

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Purpose: In Israel, ultra-Orthodox males have higher prevalence of myopia (82.2%) than their religious (50.3%) and secular (29.7%) peers, likely due to the intense near work demands and long school days in the ultra-Orthodox educational system. The Israel Refraction, Environment and Devices (iREAD) longitudinal study aimed to assess whether ultra-Orthodox boys also had higher myopic progression than their peers.

Methods: Israeli boys (N=125), ages 5-11 years, were recruited and categorized as ultra-Orthodox (UO, N=41), religious (R, N=53) or secular (S, N=41) based on the educational systems that they belonged to. Each participant underwent two comprehensive eye exams, 12 months apart, which included cycloplegic autorefraction and axial length measurement. Myopia was defined as average cycloplegic spherical equivalent of both eyes ≤-0.50D. Test statistics from paired-sample t-tests were used to assess 12-month changes in refraction and axial length, and ANOVAs and pair-wise comparisons were used to test for differences between groups. The P-values for test statistics were computed using null distributions obtained using resampling.

Results: Mean age was 8.6±1.5 years and was similar between the three groups (P=0.6). Overall, myopia prevalence increased from 32% at visit 1 to 40% at visit 2 (P=0.02), with no significant differences in the change in prevalence between groups (visit 1: UO: 44%, R: 27%, S: 25%, P=0.28; visit 2: UO: 56%, R: 35%, S: 29%, P=0.1). At both baseline and 12 months, the ultra-Orthodox group had more myopic refractions (visit 1: -0.73±1.64D, visit 2: -1.24±1.68D) than religious (visit 1: 0.08±1.19D p<0.02, visit 2: -0.22±1.36D p<0.004) and secular (visit 1: 0.21±1.16D p<0.02, visit 2: 0.07±1.23D p<0.001) groups. Over 12 months, the ultra-Orthodox group had significantly greater myopic progression (-0.51±0.47 D) than the religious (-0.30±0.39D, P=0.05) and secular (-0.14±0.28D, P<0.001) groups. Axial length significantly increased for all 3 groups (p<0.001), but without significant differences between groups (P=0.3 and P=0.1, for baseline and 12-months, respectively).

Conclusions: The study demonstrates that ultra-Orthodox boys had greater myopic progression over the course of a year than religious and secular boys. Future analysis will test if differences in behaviors of ultra-Orthodox boys related to near work and time outdoors, as previously observed in the baseline visit of the iREAD study, contributed to greater myopia progression.

Cornea, external eye disease and refraction
Rapid fire – 2 minutes

C5
AC
Or Shmueli
Hadassah Medical Center

Refractive Predictive Errors Using Barrett II, Hoffer-Q, and SRKT Formulae For Pediatric IOL Implantation

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Purpose: To compare the accuracy of the Barrett II universal (BU II) formula, Hoffer-Q, and SRKT formulae following lensectomy and IOL implantation in a large pediatric cohort.
Methods: Retrospective study of children who underwent lensectomy and IOL implantation between 2015 and 2023 at Hadassah-Hebrew University Medical Center, Jerusalem, Israel.
Results: One hundred and fifty-one eyes of 104 children aged 6.0±3.9 years were included. The mean Prediction error (PE) was -0.08±1.54 diopters (D) with BU II, 0.24±1.46 D with Hoffer-Q, and 0.71±1.92 D with SRKT (P=0.10). In eyes with axial length (AL)<22 mm, BU II and Hoffer-Q had a smaller PE than SRKT (P=0.024). In eyes with AL≥22 mm, BU II had a smaller PE than Hoffer-Q (P=0.048).
In children 24 months or older at surgery, BU II had a smaller PE than SRKT and Hoffer-Q (P=0.012). However, in younger children, no difference was found between the formulae (P=0.61).
For mean k-values ≥44.5 D, BU II and Hoffer-Q had a smaller PE than SRKT (P=0.002). An absolute prediction error <1.0 D was obtained with BU II in 66% of eyes and SRKT in 35% (P=0.01).
Conclusions: The BU II formula performed well with a small prediction error. No significant difference in PE was detected overall between the formulae. However, only BU II demonstrated a stable prediction error at varying axial lengths, K-readings, and ages. As the biometric parameters of the developing eye change with growth, the BU II formula offers a reliable and stable option for pediatric IOL calculation.

Cornea, external eye disease and refraction

Rapid fire – 2 minutes

C7

Dean David Lichter
Hadassah Medical Center

Clinical And Epidemiological Factors Affecting Donor Corneal Endothelial Cell

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Background: Cornea donor shortage remains the critical barrier to meet the demands for corneal transplantation. While age and prior cataract surgery are known to decrease donor corneal quality, a system to optimize resource allocation based on predicting corneal suitability is lacking.
Purpose: To identify factors affecting donor corneal endothelial cell count (ECC) in an Israeli eye bank, with a specific focus on the impact of the short death-to-retrieval time (DRT).
Methods: A retrospective analysis was conducted on 611 donor corneas retrieved at Hadassah Medical Center between 2018 and 2022. Univariate and multivariate analyses were employed to identify factors associated with adequate ECC (defined here as ECC≥2400 cell/mm²), including age, sex, medical history, cause of death and DRT.
Results: The mean ECC was 2625 cells/mm² (SD ±519), with 76.3% (n=466) demonstrating adequate ECC. The mean donor age was 64.4 (SD ±15.3) years. The median DRT was 2 hours and 29 minutes. Advanced donor age and pre-existing medical conditions like diabetes mellitus (DM), hypertension (HTN), ischemic heart disease (IHD), and prior cataract surgery were all significantly associated with lower ECC ($P < 0.001$). Multivariate analysis confirmed that age and history of cataract surgery were the only significant risk factors for a reduced ECC ($P<0.0001$). While a trend suggested a higher chance of adequate ECC in corneas retrieved within 4 hours of death (82.5% vs. 75%; $p=0.11$), this association did not reach statistical significance.
Conclusions: Advanced donor age, prior cataract surgery, death due to sepsis, and specific medical conditions like DM, HTN, and IHD significantly reduce corneal ECC and thus impact suitability for transplantation. Furthermore, we suggest a potential benefit of shorter DRT on corneal suitability, warranting further investigation.

C8
AC

Mattan Arazi
Chaim Sheba Medical Center at Tel HaShomer

First-in-human Clinical Trial of a Novel Eyelid warming Device in Meibomian Gland Dysfunction

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Purpose: Meibomian gland dysfunction (MGD) causes significant patient morbidity as well as economic burden. The purpose of this study was to evaluate a novel eyelid warming and a neuro-stimulating device that delivers heat via low-level infrared radiation to the eyelids of patients with MGD.

Methods: In this prospective interventional study, patients with MGD were recruited at a single medical center. The main outcome measures included changes in tear break-up time (TBUT), Schirmer's test, and Ocular Surface Disease Index (OSDI), overall satisfaction, and corneal signs of dry eye. Patients were instructed to use the device twice daily for 5 minutes on each eye for a total of 14 days. Follow-up assessments were performed after the 2-week treatment.

Results: A total of 10 patients were included; mean age was 67 ± 16 years; six males (60%). Changes in pre- vs. post-treatment TBUT (5.0-6.11), OSDI (281.1-23.9), and Schirmer score (8.67-7.11) were not statistically significant. Over a course of 243 treatments, 131 (54%) demonstrated improvement in symptoms, 40% found no change, and 6% experienced worsening of symptoms. General satisfaction was observed overall in 80% of the patients. No adverse events were observed.

Conclusions: In this first study of a novel eyelid warming device, ovFreuterall subjective satisfaction was reported in 80% of patients. Potential advantages of this user-friendly device include its ability to improve MGD and tear film stability, as well as symptomatic relief, while allowing the user to continue with normal daily functioning while undergoing treatment.

Possible correletion between chemotherapy treatment of corneal donors to lower endothelial cell quality of their grafts

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Purpose
High quality endothelial cells in corneal grafts is crucial for a successful corneal transplantation. It may be influenced by various factors like age, ocular surgeries, trauma, genetic diseases etc. Oncological treatments, such as chemotherapy and radiation therapy, may lead to cellular effects that could potentially affect the health, morphology and density of the corneal tissue. At present, there is no literature demonstrating an altered endothelial cell density and morphology associated with chemotherapy treatment of the donors. The aim of this study is to investigate whether there is a correlation between pre-mortem chemotherapy treatment and its effect on the endothelial cells.
Methods
Retrospective data of ex-vivo corneal transplants from oncology donors versus helathy donors harvested within the past decade at the Rabin Medical Center.. Data included graft's endothelial cell count, morphology, ocular and systemic history, chemotherapeutic regimen received prior to death, and history of radiation therapy to the neck and head area.
Results
Data of 471 corneal transplants from oncology treated donors (group A) versus 471 age matched, non-oncologic donors (group B) was collected. Average age at death was 65 in both groups. Average time from death to graft cell analysis was 1.1 days in group A, and 0.97 in group B (pv= 0.1). In sub-group age of 20-40, ECD was 2694 in group A vs. 2993 in group B (pv = 0.02). In ages of 50-60, ECD was 2377 in group A vs. 2656 in group B (pv = 0.006). In ages of 60-70, ECD was 2242 in group A vs. 2522 in group B (pv = 0.001). In age groups 30-40 and 70-80 there was no significant difference in regards to ECD. Radiation treatment of the oncologic donors was not significantly different than the non-oncology group.
Conclusions
Our findings suggest that oncologic treatment may lead to endothelial cell damage that could compromise the quality of the corneal grafts and possibly the outcomes of their correspondant transplant surgeries. these findings could contribute to better understanding the impact of oncological treatments on corneal health and guide the selection of suitable corneal grafts for transplantation, thereby improving the overall outcomes of corneal transplantation procedures for patients with a history of oncological treatments. To the best of our knowledge, this is the first study assessing the effect of chemotherapy treatment prior-to-death of corneal donor to their graft overall quality

Accelerated CXL versus accelerated contact lens–assisted CXL for progressive keratoconus in adults

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Purpose: The purpose of our study was to compare the clinical and tomographic properties of adult patients with keratoconus treated with accelerated corneal cross-linking (A-CXL) versus accelerated contact lens–assisted corneal cross-linking (A-CACXL).

Methods: Patients were enrolled who underwent A-CXL and A-CACXL due to progressive keratoconus from January 2015 to 2018 in this retrospective case–control study. The treatment group (minimum corneal thickness of less than 400 µm after epithelium removal; 30 patients, 30 eyes) was treated with ACACXL; the control group (minimum corneal thickness of 400 µm or greater, 32 patients, 32 eyes) was treated with A-CXL. Assessments occurred before treatment and 3-year postoperatively. Demographic, clinical, and tomographic data were obtained from outpatient clinic reports.

Results: Significant improvement in visual acuity was evident at 3-year follow-up for the control group in uncorrected distance visual acuity (0.63 ± 0.41 vs 0.44 ± 0.28 logMAR, P = .031) and the treatment group in corrected distance visual acuity (0.51 ± 0.30 vs 0.33 ± 0.34 logMAR, P = .03. Progression of keratoconus was halted at similar rates for both groups (73% treatment, 87% control, P = .2).

Conclusions: A-CACXL halted keratoconus progression in 73% of eyes and achieved regression in 37% of eyes, with rates comparable to A-CXL. Visual outcomes improved for both groups, with similar keratometry changes. A-CACXL is an effective and safe option for patients with keratoconus and thin corneas, with results similar to A-CXL treatment in patients with a minimum corneal thickness of 400 µm or greater.

Fire ant punctate keratopathy in companion animals. 100 canine and feline cases

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Purpose: Fire ant punctate keratopathy (FAPK) is a unique corneal lesion that has been reported in many warm countries. It appears to be uncommon in Israeli patients, described in a single case series of 4 patients (Patael et al., 2009), However, it is very common in companion animals This study describes ocular findings in 100 Israeli dogs and cats diagnosed with FAPK Methods: Affected animals underwent a comprehensive ophthalmic examination. Patient demographics and clinical findings were recorded. Results: Based on the presence of round, white, fluorescein negative anterior stromal lesions, FAPK was diagnosed in 84 dogs and 16 cats, with mean ±SD ages of 6.5 ±3.7 and 5.9 ±4.6 years, respectively. FAPK was the presenting complaint in 15/84 dogs, and progression and transient irritation were reported in 3/84 and 15/84 dogs, respectively. Most dogs lived in apartments (60%), were systemically healthy (82%), and had additional ocular diseases (74%). FAPK was unilateral in 60/84 dogs, with 1-3 and >3 lesions recorded in 46/108 and 62/108 affected eyes, respectively. Most lesions were in the central cornea and ranged in diameter between 0.5-7.57 mm. FAPK was the presenting complaint in 2/16 cats, and progression and transient irritation were reported in 1/16 and 2/16 cats, respectively. All cats lived indoor/outdoor, 73% were systemically healthy and 50% had additional ocular disease. FAPK was unilateral in 12/16 cats, with 1-3 and >3 lesions recorded in 9/20 and 11/20 affected eyes, respectively. Lesions were scattered throughout the cornea and were pinpoint to 5 mm in diameter. Dermatological disease was not present or reported in the history of any animal. Conclusions: As in human patients, FAPK is a differential diagnosis for transient ocular irritation in dogs and cats. Most lesions don't progress. The cause of FAPK in animals remains unproven, though an association with fire ants has been proposed in humans. Companion animals may serve as a sentinel surveillance tool for FAPK in Israeli households.

Teprotumumab As a Potential Therapy For Human Pterygium

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Purpose: Pterygium, characterized by a wing-shaped overgrowth of conjunctival and fibrovascular tissue on the cornea, can lead to astigmatism and corneal scarring. Surgical removal is the standard treatment, yet it often results in painful recovery and a risk of recurrence. This study evaluates in vitro the potential therapeutic effect of Teprotumumab (TPT, Tepezza®), an IGF-1R blocking monoclonal antibody, on pterygium fibroblasts.

Methods: In compliance with the Helsinki Declaration and with proper informed consent, pterygium specimens were surgically collected and cultured. Pterygium fibroblasts were isolated and characterized using phase-contrast microscopy and immunofluorescence. Gene expression for growth factors signaling, angiogenesis, and extracellular matrix modifier genes were examined using qPCR in both untreated and TPT-treated pterygium fibroblast cell cultures (n=5, each). Electron microscopy (EM) provided detailed insights into the pterygium's microstructure.

Results: EM demonstrated the presence of a large number of pterygium fibroblasts, stromal invaginations, abundant collagen fibers, and blood vessels in the untreated pterygium tissue. Pterygium fibroblasts were validated using phase-contrast microscopy (flat, spindle shape with a distinct nucleus) and immunofluorescence (vimentin-positive and CD31-negative). TPT treatment led to an average of 40% reduction in pterygium fibroblast viability (n=5).
Comparison of gene expressions with the untreated cells showed that TPT significantly reduced FGF2 by 0.77-fold (± 0.12-fold, p= 0.0046), IGF1R by 0.80-fold (± 0.18-fold, p=0.1), VEGFA by 0.66-fold (±0.07-fold, p=0.00001) and PAI-1 by 0.45-fold (±0.18-fold, p=0.0003). Interestingly, TPT significantly increased the expression of MMP3 by 2.59 fold (± 0.78-fold, p=0.0035) and MMP2 by 1.48 fold (± 0.39-fold, p=0.043).

Conclusions: The structural analysis via EM highlighted the distinct fibroblast architecture within pterygium tissue. TPT's application markedly reduced fibroblast viability and altered gene expression, suggesting a potential therapeutic role. The significant modulation of gene expression and cell viability associated with TPT treatment underscores the need for further in-depth molecular and functional studies to ascertain its efficacy in treating pterygia.

Factors Influencing Consent for Corneal Donation: Insights from a Prospective Study

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Purpose: This study aimed to identify factors influencing consent for corneal donation among potential donors, thereby shedding light on determinants crucial for enhancing donation rates.

Methods: A prospective study conducted at Hadassah Medical Center from 2019 to 2022, included 824 deceased patients eligible for corneal donation. Families were approached for consent, with data collected on decision outcomes, next-of-kin approached, contact methods (face-to-face or phone), and religiosity profiles (secular, modern orthodox, ultra-orthodox, traditional). Clinical and epidemiological factors, such as time and cause of death, age, religion (Jewish, Muslim, Christian, and others), and hospitalization department, were extracted from medical records. Univariate and multivariate analyses were performed to identify factors associated with higher consent rates.

Results: Among 824 families approached, 30.7% consented to corneal donation. Religion significantly impacted consent ($p<0.001$), with Jewish families exhibiting the highest consent rate (36.7%, OR 6.58). Religiosity also played a significant rule ($p<0.001$), with secular families demonstrating the highest consent rate (57.3%, OR 6.98), followed by modern orthodox (53.6% OR 6.57). Families of potential donors from the Emergency Room displayed the highest consent (52.2% OR 1.77, $p=0.001$), while Departments of Internal Medicine exhibited the lowest (26.3%, OR 0.49). The identity of the next-of-kin approached significantly impacted consent ($p<0.05$), with spouses exhibiting a higher likelihood of consent (44.7%, OR 1.63) compared to other family members. No significant difference in consent rates was observed between direct approach and phone calls ($p=0.80$). Forward stepwise analysis revealed that religiosity was the most significant factor influencing consent decisions ($p < 0.0001$). Conversely, other variables did not significantly affect consent decisions.

Conclusions: Religion, religiosity, next-of-kin approached, and department of hospitalization emerged as pivotal factors influencing consent for corneal donation. Additionally, the study highlights the comparable efficacy of phone-based approaches in obtaining consent, providing insight for refining donation outreach strategy.

Prevalence and Risk Factors of Keratoconus in Israeli Arabs

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Purpose: The study aimed to determine the prevalence of keratoconus (KC) and detect the risk factors for developing KC among the Arab population in Israel.
Methods: The prospective cross-section cohort study included corneal topography and questionnaires about possible risk factors for developing KC. The inclusion criteria included Arab patrons above the age of sixteen. The study excluded participants with a history of spherical or astigmatic soft contact lenses or rigid gas-permeable contact lenses, including orthokeratology lens use. Corneal topography was conducted, and questionnaires were filled out by the subjects at shopping centers in Beit Hanina-Jerusalem, Yaffo-Tel Aviv, Baqa al-Gharbiyye, Umm el-Fahem, Kafr Kanna, Sakhnin and Kafr Yasif between January 2022-January 2024.
Results: 13,917 subjects participated in the study. The average age was 32.67±6.63 years (ranging from 17 to 43 years, 52.83% male) and 30.32±8.15 years (ranging from 16 to 50 years, 49.40% male) of normal subjects and KC subjects, respectively. The prevalence of KC was 1.0 to 261.58 population (95% confidence interval (CI): 1.0 to 221–359) The leading odds ratio (OR) were 11.71 (95% CI: 6.5957 to 20.8100, $P < 0.0001$), 3.922 (95% CI: 2.2575 to 6.8158, $P < 0.0001$) and 3.20 (95% CI: 1.7104 to 6.0102, $P = 0.0003$) for family history of KC, eye rubbing, and atopic dermatitis, respectively. Exposure to the sun or UV exposure was not found to be a risk factor.
Conclusions: This study reveals a significant prevalence of KC among the Arab population in Israel, alongside identifying key risk factors.

Changes in focal Rod-, Cone- and Melanopsin-mediated pupil light responses associated with Parkinson disease progression

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Purpose:
To investigate the changes in pupil light reflex (PLR) mediated by rods, cones, and melanopsin-expressing intrinsically photosensitive retinal ganglion cells (ipRGCs) associated with disease progression in Parkinson Disease (PD) patients.
Methods: 12 PD patients completed a baseline and two-year follow-up visits. All patients underwent: (1) A neurological assessment of PD stage and progression according to the MDS Clinical Diagnostic Criteria for PD; (2) Genetic mutation analysis; (3) Chromatic Pupilloperimeter testing under mesopic light adaptation conditions to assess the PLR for small (0.43°) red and blue light stimuli presented at central (4.2°) and peripheral (21°) visual field locations.
Results:
Significant decline was identified in rod-mediated maximal pupil contraction (PPC), with a mean decrease of 19.6% between the baseline and 2-year follow-up visit across central and peripheral retinal locations ($p = 0.01$). The cone-mediated PPC was reduced by a mean of 18.7% ($p=7 \times 10^{-7}$). Moreover, the melanopsin-mediated PLR across central and peripheral retina was substantially reduced in the two-year visit ($p= 3.04x10^{-5}$ compared with baseline).
Conclusions:
The intrinsic and extrinsic light responses of ipRGCs deteriorated with disease progression in PD patients. These findings underscore the potential use of chromatic pupilloperimetry as a valuable tool for objective monitoring of PD disease progression.

Comparative Study of Near Work Behaviors Among Ultra-Orthodox and Non-Orthodox Jewish Male College Students

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Purpose: Ultra-orthodox Jewish men are known to exhibit a high prevalence of myopia, potentially due to intense near work. Our recent study showed that, under laboratory conditions, ultra-orthodox men engage in reading and tablet use at significantly closer distances than their non-orthodox counterparts. This study aims to investigate the visual behaviors of ultra-orthodox and non-orthodox male students under real-life campus conditions.

Methods: A total of 29 ultra-orthodox (age 24.8 ± 4.4 years) and 37 non-ultra-orthodox (age 23.8 ± 4.3 years) male students participated in the study. Autorefraction (VX130/l80, Luneax) and visual acuity were measured. An objective range-finding sensor (Clouclip) was mounted on the spectacles of participants, who wore them for at least one day while studying on the college campus. Viewing distances were categorized as follows: overall near work (10-99 cm), very-near work (10-39 cm), and intermediate near work (40-99 cm). Statistical analyses included Student's T-tests and Mann-Whitney U tests to compare groups.

Results: The ultra-orthodox group showed a significantly higher myopic refraction (-4.05 ± 3.9D) compared to the non-ultra-orthodox group (-1.90 ± 2.4D, $p<0.02$). A significantly shorter overall near viewing distance was observed for the ultra-orthodox (41.5 ± 7.7cm) compared the non-ultra-orthodox group (48.2 ± 7.8cm, $p<0.0001$). The very-near work viewing distance was also shorter for the ultra-orthodox (27.0 ± 2.8 cm) compared to the non-ultra-orthodox group (28.6 ± 2.4 cm, $p>0.02$), with no significant differences in intermediate near distances (58.1 ± 4.9 for ultra-Orthodox, 59.9 ± 4.8 cm for non-ultra-orthodox, $p=0.14$). Although, there was no difference in the time spent at overall near work distance between the groups (ultra-orthodox: 57± 13% vs. non-ultra-orthodox: 55 ± 16%, $p=0.56$), the ultra-orthodox spent more time in very-near work (ultra-orthodox: 32 ± 15% vs. non-ultra-orthodox: 21± 12%, $p<0.005$), and less time at intermediate near distances (ultra-orthodox: 25± 12% vs. non-ultra-orthodox: 34 ± 13%, $p<0.006$).

Conclusion: During campus studies, ultra-orthodox students were observed to work at significantly shorter viewing distances and spent considerably more time engaged in very-near work compared to their non-ultra-Orthodox peers. These findings suggest that intensive near-work activities may be a contributing factor to the myopic trends within this community.

COLOR VISION TESTING – COMPARING ISHIHARA BOOKLET TO SMARTPHONE APPLICATIONS

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Purpose. Evaluation of color vision, an important component of visual function, is commonly performed using the pseudoisochromatic Ishihara plates. During the recent decade Color vision tests applications became widely available and are widely used even though they have not yet been validated in the literature. The aim of this study was to compare the standard Ishihara booklet with color-vision-testing smartphone applications.
Methods. A prospective observational study on 42 normal trichromate subjects and 32 patients with optic neuropathy, compering Ishihara test booklet, the Color Vision Test application (CVT app) and the Eye Handbook application (EHB app).
Results. In healthy subjects, no statistically significant difference was found between the Ishihara test and the CVT app, though, the percentage of correct answers on the EHB test was higher compared to the Ishihara test (difference of 4.0% for right eyes, p=0.000 and 2.3% for left eyes, p=0.008).
All tests were able to differentiate between a healthy eye and an optic neuropathy eye by comparing correct number of answers. The percentage of correct answers on the Ishihara test was significantly higher than in the CVT app, both in healthy eyes (89.5% and 82.0% respectively, P= 0.04) and in eyes with optic neuropathy (62.3% and 51.4% respectively p=0.02).
In the EHB app, there was a significant difference between the healthy eye and the optic neuropathy eye in all plates except plate number 5, in which the statistically significant difference was borderline (p = 0.07).
ROC curve analysis found AUC for Ishihara, CVT and EHB of 0.736, 0.812 and 0.778, respectively, but with no statistically significant except the difference in AUC between Ishihara and the CVT that was almost significant (p = 0.051).
Correlation was found between the percentage of correct answers and VA and VF MD.
Conclusions. The smartphone applications tested have different sensitivity for detection of color vision deficiency in patients with optic neuropathy compared to Ishihara booklet, limiting their usefulness for clinical use. Further validation of these applications is required.

Adjusting for Reproducibility Limit Can Modify RNFL Thickness Color Coding\

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Purpose: The retinal nerve fiber layer (RNFL) thickness is commonly color-coded based on the percentiles of the normative database. We evaluated how accounting for the reproducibility limit of RNFL thickness measurement can affect the color coding of sectoral circumpapilary RNFL (cpRNFL) thickness.
Methods: Optical coherence tomography disc cube scans (Carl Zeiss Meditec, Dublin, CA, USA) were collected from 173 consecutive patients (346 eyes) tested from 15/10/23-15/11/24. The color codes for each of four cpRNFL quadrants as well as the six Garway-Heath (GH) sectors were obtained from the commercial report. The color codes based on thickness value (TV) were compared to those based on thickness minus reproducibility limit (TMRL) and thickness plus reproducibility limit (TPRL).
Results: Based on TV, there were 1,181 green (>5th percentile) quadrants and 1,637 green GH sectors. Based on TMRL color codes, 133 (11%) and 156 (13%) of these quadrants changed to yellow (≥1st and ≤5th percentiles) and red (<1st percentile) respectively. In the GH sectors analysis sectors, 197 (12%) converted to yellow and 51 (3%) to red. All 57 yellow quadrants based on TV changed to green in the TPRL scheme and to red in the TMRL scheme. Of the 146 yellow GH sectors based on TV 140 (95%) transitioned to red in the TMRL scheme and 144 (98%) shifted to green in the TPRL scheme. All 146 red quadrant remained red in the TPRL scheme. However, of the 293 red GH sectors based on TV, 98 (33%) became yellow, and 43 (14%) became green in the TPRL scheme. Among the six GH sectors, greatest agreement between color coding schemes was observed at the superotemporal (ST) and inferotemporal (IT) sectors. The percentile range (based on the difference between the percentiles of the TPRL and TMRL) was similar in green quadrants and sectors. However, for reds, the percentile range was narrower in quadrants compared to GH sectors ($P<0.001$).
Conclusions: Accounting for the reproducibility limit can affect the interpretation of cpRNFL thickness color coding. Red quadrants and sectors were found to be the most consisted of the GH sectors, the ST and IT sectors remained the most consistent. Both quadrants and GH sectors colored yellow based on TV were most likely to change in both the TPRL and TMRL schemes. Our findings suggest that using the reproducibility limit has the potential to reduce both over and underdiagnosis of pathologic cpRNFL thinning and might help explain the limitation of using such RNFL metrics for glaucoma screening."

Elevated Iron Levels In Tears of Patients Diagnosed With WDR45 X-Linked Optic Atrophy

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Purpose: Pathogenic variants in WDR45 are associated with iron deposits in the basal ganglia and optic atrophy. This study aims to report the measurement of iron levels in the tears of patients diagnosed with WDR45 X-linked optic atrophy as compared to healthy controls.

Methods: Tear samples were collected from the inferior fornix using Schirmer filter strips and analyzed for trace elements. Measurements by Particle Induced X-ray Emission (PIXE) analysis were focused on iron levels. The study group included 3 patients from two families - two brothers, ages 26 and 32, and a 3-year-old female. All patients were genetically diagnosed with a novel pathogenic variant in the WDR45 gene, and all demonstrated optic atrophy.
A group of 40 healthy subjects consisting of 33 females and 7 males, ages 17-63 years (mean 31.44 years) served as a control group. The samples were analyzed by PIXE analysis using an ion accelerator. The iron levels in the tears were calculated as the difference between the patients and the mean control group. A similar calculation was taken for all the other trace elements in the tears.

Results: High iron levels were measured in the tears of the two brothers diagnosed with WDR45 X-linked optic atrophy, but not in the 3-year-old girl. No differences were detected for other elements.

Conclusions: This study is the first to reveal high iron levels in the tears of patients diagnosed with X-linked optic atrophy due to WDR45 mutation. The findings broaden our understanding of WDR45 iron-related disorders pathophysiology, and the clinical findings may provide evidence of iron deposition in the brain. Future applications in clinical practice may benefit patient care.

Role of Visual Evoked Potential and Ocular Trauma Score as Predictors of Visual Recovery in Eye Globe Injuries

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Purpose: To evaluate the effectiveness of visual evoked potential (VEP) and ocular trauma score (OTS) in predicting visual potential among cases of globe trauma not involving the optic nerve.

Methods: This was a retrospective cohort study that analyzed clinical data from eye globe injury cases undergoing flash VEP between January 2000 and May 2021. Inclusion criteria: flash VEP completion within 48 hours, pre-surgical intervention. Exclusions: head trauma, optic nerve injuries. Abnormal VEP: <7 µV amplitudes, >120ms latencies. The OTS was computed, and penetrating injuries were categorized.

Results: Of 85 eyes meeting inclusion criteria, mean age was 31.9±20.6 years, with 82.4% male. Median follow-up: 22 months (range 3-35). Baseline mean LogMAR best corrected visual acuity (BCVA) was 2.48±1.69 and follow-up was 2.36±1.89 (p=0.663). OTS correlated inversely with ocular penetration extent (Spearman's rho -0.672, p<0.0001), VEP signal amplitude (Spearman's rho -0.320, p=0.025), and LogMAR change in BCVA at follow-up (Spearman's rho -2.87, p=0.022). VEP signal amplitude (and not latency) inversely correlated with maintaining or improving visual acuity at follow-up (Spearman's rho -0.249, p=0.042). Positive predictive value (PPV) for normal VEP predicting maintained or improved visual acuity was 75.6%, with a negative predictive value (NPV) of 21.3%. In blunt trauma cases, baseline VEP amplitude results demonstrated superior predictive value with a higher PPV (100% vs. 46.7%) and a lower NPV (19.2% vs. 23.1%) when contrasted with cases of penetrating injury. In 12 eyes with no recordable VEP signal, final BCVA was no light perception in 7/12, light perception in 4/12, and hand motion in 1/12.

Conclusions: In cases of traumatic eye injuries confined to the globe, this study unveils a correlation between VEP signal amplitude (as opposed to latency) and OTS with visual outcomes. Therefore, OTS could serve as a reliable substitute for VEP, aiding in predicting visual outcomes. Moreover, in instances of blunt trauma, baseline VEP amplitude demonstrates superior predictive accuracy compared to penetrating injuries.

Comparison of inter and intra-rater reliability of the measurement anisocoria using optical coherence tomography and a smartphone camera

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PURPOSE: Detection of anisocoria can aid in the early diagnosis of life-threatening conditions. In dark lighting conditions, in young patients, and when examining patients with dark irides. This study aimed to assess and compare the inter and intra-rater reliability of anisocoria assessments using near-infra-red OCT and smartphone photos.

METHODS: Binocular photos of the eyes of the participants were taken using OCT and a smartphone camera, after applying Tropiacmide 0.5% drops to create artificial anisocoria. 358 photos were presented in random order to three optometrists who were asked to manually measure the diameter of each pupil in each photo using a PD ruler.
Inter and intra-rater reliability for the measurement of anisocoria was analyzed using interclass and intraclass correlation coefficients (ICC). Inter and intra-rater agreement on the presence of anisocoria of one mm or more were assessed using Fleiss and Cohen Kappa.

RESULTS: The inter and intra-rater reliability of anisocoria measurements using the OCT was excellent in all age, eye color, and sex groups (ICC 0.93-0.99, $p<0.001$). The smartphone measurements were less reliable (ICC=0.84-0.90, $p<0.001$) and reliability decreased significantly photos of dark-eyed participants (ICC=0.36-0.82, $p\leq0.009$).
Using Kappa, there was excellent inter and intra-rater agreement on the presence of anisocoria of one mm or more in the OCT photos ($k=0.83-1.0$, $p\leq0.001$). Agreement from the smartphone photos was lower ($k=0.53-0.74$, $p<0.0001$) and decreased in the dark-eyed group ($k=0.11-0.47$, $p\leq37$).

CONCLUSION: The OCT allows for a highly reliable assessment of anisocoria regardless of eye color, age, and sex. The use of a smartphone for the assessment of anisocoria, while convenient, is a considerably less reliable method and this study's findings lead us to recommend that OCT photos should be used for the assessment of anisocoria in clinical settings, when possible, especially for patients with dark irises.

Longitudinal optical coherence tomography indices in pediatric idiopathic intracranial hypertension

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Purpose: Idiopathic intracranial hypertension (IIH) may result in optic nerve fiber loss and even atrophy. The exact timing of the optical coherence tomography (OCT) indices reaching nadir and the factors that predict the patient's anatomical outcome are not known in the pediatric population. We aimed to determine the timing of a nadir finding and the factors that affect nadir retinal nerve fiber layer (RNFL) thickness values in the pediatric IIH population.

Methods: The medical records of all pediatric IIH patients (Age<17 years) who were treated in our institution from December 2009 to January 2023 were retrospectively reviewed. The following data were recorded at baseline and at nadir OCT finding: lumbar puncture opening pressure, body mass index (BMI), visual acuity, visual field mean deviation (MD), OCT RNFL, ganglion cell complex (GCC) values, and management.

Results: Twenty of the 23 patients (87%) were female, the cohort's average age was 12.7±3.5 years, and their mean BMI was 25.8±6.9 kg/m2. The mean RNFL thickness at presentation was 307.4±125.3 μm. The mean time to nadir was 5.9±2.9 months. The average RNFL and GCC thickness at first nadir OCT appearance were 101.7±16.3μm, and 81.7±6.9 μm, respectively. The nadir average RNFL thickness negatively correlated with age (r=-0.43, P=0.04) and BMI of patients (r=-0.38, P=0.09). The time to nadir was negatively correlated with baseline HRR (r=-0.42, P=0.04) and the initial Uramox dose of patients (r=-0.39, P=0.06). The mean follow-up was 40.7±33.7 months, during which 6 (26.1%) patients sustained a recurrent IIH episode.

Conclusions: Our results showed that the final anatomical outcome of IIH episodes resulted in RNFL and GCC thinning, and that it was reached after a mean of 5.9±2.9 months, which is shorter than the time to nadir in adults. The time to RNFL nadir and its values correlated with younger age and lower BMI, indicating that pediatric IIH patients have unique characteristics that should be considered during follow-up and treatment of these patients.

Analysis of the anatomical and functional ocular changes related to spaceflight

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Purpose: To describe novel early changes in ocular physiology following a short duration exposure to microgravity - A case report

Methods: The AX-1 mission was sent to the International Space Station by AXIOM Space and NASA in April 2021 for 17 days. A 64-year-old male astronaut participated in our study. We conducted before and after-spaceflight full ophthalmic examination and multimodal imaging sessions that included anterior and posterior segment imaging and head MRI. Optical coherence tomography angiography (OCTA) imaging is not a standard NASA protocol and was conducted for the first time in history. Automated image processing was used for accurate quantification of the flow signal pixels from either the retina or the choroid for separate analysis.

Results: In our study, OCT angiography studies demonstrated a significant decrease in the macular choroidal and retinal flow signal of 29% and 8.5% respectively in the right eye and 11% and 6.5% respectively in the left eye after the spaceflight as compared to baseline ($p<0.0001$ both eyes). Focal alterations in choroidal thickness and Haller vessels diameter were noted but did not reach statistical significance. Mild widening of the optic nerves sheathes were found on MRI. No other alternations were found in structures or functions. The astronaut reported a need for reading glasses while in space.

Conclusions: Significant alternations in macular choroidal blood flow were after a short duration spaceflight. These should be further studied as possible biomarkers for Spaceflight-Associated Neuro-Ocular Syndrome (SANS).
We recommend that future spaceflights include OCTA imaging as a standard protocol.

Use of Topographical Structure–Function Agreement For Glaucoma Screening

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Purpose: To evaluate a topographical approach for glaucoma screening using a Structure-Function (S-F) combined report in a real-world clinical setting.

Methods: The S-F reports were collected from individuals seen at a tertiary glaucoma clinic between 11/15/23-10/15/23. The S-F report combines the 24-2 visual field (VF) pattern deviation points with the six retinal nerve fiber layer (RNFL) zones of the Garway-Heath sectors.[1] Each zone is color-coded based on the deviation of the mean RNFL thickness from the age-corrected reference database (i.e., green indicates areas of RNFL thickness within normal limits, yellow indicates deviations from normal with $P < 5\%$, and red indicates deviations with $P < 1\%$). The reference standard (RS) was determined by a glaucoma specialist (AL). Eyes were classified using the Columbia University OCT-based Method (CU-method) for glaucoma detection [2] as glaucomatous optic neuropathy (GON, N=79), OCT glaucoma suspect (GS, N=21), or not glaucoma (NG, N=138). For this study, we recorded the color and the number of abnormal ($P<2\%$) VF points of each RNFL zone. Different combinations of abnormal VF and abnormal RNFL criteria were evaluated. The optimal criteria were defined based on the percentages of abnormal structure–abnormal function (aS-aF) agreement found in GON eyes and “no aS-aF” found in NG eyes.[3]

Results: A criterion of “At least one yellow RNFL zone that has two or more abnormal VF points” yielded the strongest agreement with the RS (Kappa = 0.90) having excellent “no aS-aF” agreement for the NG eyes (98%) and good aS-aF agreement for the GON eyes (90%). In 68 of the 71 GON cases (96%) that were detected, aS-aF agreements was observed in either the superior-temporal (ST) zone (14, 21%) inferior-temporal (IT) zone (16, 24%) or both (38, 56%). Eight of the 76 GON eyes were below the “best” criteria threshold. The lack of structure-function agreement was due to structural damage without a detectable functional loss on the 24-2 pattern deviation map (5) and vice versa (2). In the remaining case, the abnormal VF cluster fell outside the boundaries of the abnormal RNFL zone.

Conclusions: A S-F report may be useful for ruling out glaucoma and has the potential to assist in detection of the disease. Early glaucoma detection might be limited due to lower S-F agreement in such cases. The ST and IT zones were the most sensitive to glaucoma damage, consistent with previous reports.[4]

Reffs:
[1] Garway-Heath et al. Ophthalmology, 2000
[2] Hood et al. PRER 2022
[3] Tsamis et al. TVST 2020
[4] Hood et al. PRER 2013
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Long-term impact of carotid endarterectomy on choroidal and choriocapillaris perfusion. The INFLATE study

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Purpose: To examine the long-term effects of carotid endarterectomy (CEA) for clinically significant carotid artery stenosis (CAS) on choroidal and choriocapillaris (CC) circulation using swept-source optical coherence tomography angiography (SS-OCTA).
Design: Prospective observational study.
Participants: Patients with clinically significant CAS undergoing unilateral CEA.

Methods: SS-OCTA scans were performed on both eyes at three different time points: baseline (before CEA), within a week post-CEA (short-term follow-up [FU]), and at least 30 days post-CEA (long-term FU). Using validated algorithms, we measured mean choroidal thickness (MCT), choroidal vascularity index (CVI), choroidal vessel volume (CVV), CC flow deficit percentage (CC FD%), and CC thickness within the 5-mm circle centered on the fovea for both the eye ipsilateral to CEA (surgical side) and the contralateral eye (nonsurgical side). Multivariable regression analysis was conducted to evaluate the impact of baseline demographic and clinical factors on the changes in choroidal and CC parameters.

Results: The study included 58 eyes from 29 patients. Significant immediate improvements in MCT (P<0.001) and CC thickness (P=0.006) were observed post-CEA on the surgical side. Long-term FU showed sustained increases in MCT compared to baseline (P=0.02), while CC thickness returned to baseline levels (P=0.10). The CVI showed consistency over time, remaining unchanged in both short-term (P=0.45) and long-term (P=0.07) FUs when compared to the baseline on the surgical side. While CVV demonstrated a rise immediately post-CEA (P<0.001), this was not sustained in the long-term evaluation (P=0.06). No significant improvement in CC FD% was observed at any time point (short-term P=0.91, long-term P=0.65). The nonsurgical side only
showed a significant reduction in CVI at the long-term FU compared to before CEA (P=0.01). Clinical variables such as age, degree of stenosis, diabetes, hypertension, and smoking status did not significantly impact the changes observed.

Conclusions: CEA demonstrates a lasting beneficial effect on choroidal circulation, as evidenced by sustained increases in MCT on the surgical side over time. However, the initial improvement in CC perfusion observed immediately post-CEA is not maintained in the long term.

Vitreous and blood biomarkers associated with proliferative diabetic retinopathy

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Purpose: Uncontrolled or long-standing diabetes can lead to proliferative diabetic retinopathy (PDR), significantly impairing vision. A subset of patients does not respond adequately to conventional therapies, such as intravitreal injections of anti-vascular endothelial growth factor (VEGF), with or without laser treatment. This study aims to identify biomarkers for possible alternative treatment pathways in the vitreous and blood of patients suffering from severe PDR.

Methods: Vitreous samples were collected from PDR patients (n=3) undergoing vitrectomy for vitreous hemorrhage and control patients (n=7) undergoing ocular surgery for epiretinal membrane or macular holes. Blood samples were collected from a different group of PDR (n=3) and non-diabetic control patients without retinopathy (n=2). Medical history, focusing on diabetic control and treatment, was collected. Patients' medical records, ocular exams, responses to treatment, and imaging results were analyzed. Two-stage real-time quantitative polymerase chain reaction was used to evaluate levels of mRNA expression of genes possibly implicated in PDR including HIF2A, PAI-1, TIE1, TIE2, ANGPT2, and VEGFA. Molecular, clinical, and statistical analyses were performed comparing PDR and control vitreous and blood samples.

Results: PDR patients whose vitreous were analyzed included 2 females and 1 male, aged 71-77 (mean 74). All had pan-retinal photocoagulation treatment, and two had anti-VEGF injections before vitrectomy. All had elevated HbA1c levels. Targeted vitreous gene expression analysis revealed increased expression levels of all genes examined except for TIE1 in the PDR group. TIE1 expression levels were reduced in PDR vitreous by 0.82-fold (± 0.31), HIF2A increased by 1.45-fold (± 0.55), PAI-1 increased by 1.51-fold (± 0.64), TIE2 increased by 1.18-fold (± 0.12), ANGPT2 increased by 2.18-fold (± 0.64), and VEGFA increased by 2.76 fold (± 1.40). Likewise, in PDR blood samples, TIE1 expression levels were reduced by 0.72-fold (± 0.20) and TIE2 increased by 1.72-fold (± 0.52), while other genes' expression was not significantly altered.

Conclusions: Vitreous sample analysis revealed a trend of increased levels of HIF2A, PAI-1, ANGPT2, TIE2, & VEGFA and decreased levels of TIE1 in patients with PDR. Likewise, PDR blood sample analysis revealed a trend of increased levels of TIE2 expression and decreased levels of TIE1. This trend should be validated in a larger group of patients, to explore alternative pathways for targeted treatment.

Development and progression of geographic atrophy under anti-VEGF treatment in eyes with neovascular age macular degeneration: a quantitative fluid approach

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Purpose: To investigate the prevalence and progression of geographic atrophy (GA) lesions in patients with neovascular age-related macular degeneration (nAMD) undergoing anti-VEGF therapy in relation to quantitative retinal fluid volumes and distribution.

Methods: We utilized retrospective data from the Tel-Aviv Medical Center (TLVMC) nAMD dataset to identify eligible patients. The study included 150 patients with a minimum follow-up of 24 months. Optical coherence tomography (OCT) scans were analyzed using a deep learning tool, the NOA OCT analyzer, which automatically analyses OCT volume scans and quantifies nAMD-related activity measures. NOA provides 115 variables for a detailed analysis of retinal compartments. Near-infrared images, supported by OCT images, were used to identify and quantify areas of GA and their progression during follow-up.

Results:
At the time of nAMD diagnosis, a proportion of 17.3% of eyes presented GA, which increased to 64% after 24 months. The mean area of GA increased by 1.41 ± 3.01µ2 in 24 months. Multifocal GA was statistically significantly associated with GA development ($p<0.001$). Neither the baseline fluid status (presence of either subretinal or intraretinal fluid or combined presence of both) nor the respective baseline fluid volumes showed a significant association with GA development and progression ($P> 0.05$). When comparing the fluid volumes within the central 6mm and 3mm diameters, the only significant finding was for the subretinal 3mm volume, which showed a negative association with GA development (P-value of <0.001).

Conclusions:
A substantial portion of patients with nAMD develop GA within two years. While multifocal GA at baseline predicted progression, baseline retinal fluid status and volume had minimal impact. We will present novel data on the influence of retinal fluid fluctuations over 24 months. These findings emphasize the importance of GA monitoring in nAMD management and warrant further investigation.

Electrophysiological based investigation of hypothermia effect on the feasibility of retinal resuscitation following ischemia.

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Purpose: Previous studies have shown that the deleterious effects of ischemia on retinal functionality can be alleviated by hypothermia. Here, we further highlight this effect by thoroughly investigating the effect of hypothermia on electrophysiological functionality resuscitation following prolonged ischemia.

Methods: Using an isolated retina of a wild-type rat we investigated the effect of hypothermia on ischemia damage (15-240min at 21 or 37°C). Ischemia was induced at both the complete eyeball (following the desired treatment the retinal was isolated in an oxygenated solution) and the isolated retina level (on-chip ischemia in which the supply of oxygenated medium was switched on and off; oxygen content was found to be 13.5 mg/L and 8.7mg/L respectively). Next, several electrophysiological response features induced by 1sec flashes were investigated, namely: the number of active RGCs, the firing rate of the RGCs, and the amplitude of the various components of the electroretinogram.

Results: On-chip experiments revealed that the percentage of cells whose response was restored following an ischemia of 15min at 37C period was ~100% decreasing to ~50% for 60min and to almost 0% for 120min (p for trend =0.03). A significant decrease in the firing rate was also observed (p for trend <0.001). These results also revealed the more deleterious effect of ischemia on the OFF compared with the ON responses. A similar effect on the ERG amplitudes was also observed. At the complete eyeball level, we found a significant prolongation in the persistence of light-induced responses from 30min ischemia (under 37°C) to 240min (under 21°C).

Conclusion: A model facilitating the investigation of ischemia-induced damage and the feasibility of response resuscitation through various interventions at the single-cell level was introduced. Further investigations are required to understand the effects at the molecular level.

The clinical characteristics and outcome of patients undergoing consecutive PPV with silicone oil for failed surgery for RD

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Purpose: To describe the clinical characteristics and outcome of patients undergoing consecutive pars plana vitrectomy (PPV) with silicone oil for failed surgery for retinal detachment (RD).

Methods: A retrospective cohort study including patients with RD who underwent their second PPV with silicone oil surgery between 2010 to 2022 at Sheba Medical Center.

Results: Seventeen patients underwent PPV with silicone oil for their first and second RD surgery. The mean LOGMAR before the first surgery in the unaffected and affected eyes was 1.12 and 3.15, respectively.
Twelve (80%) patients had total RD before the first surgery, 6 (35%) had PVR. Visual acuity (VA) improved significantly (p=0.03). After the first surgery, 4 patients (24%) developed total RD, and the rest (76%) had subtotal RD. Eight (47%) developed PVR. During the second surgery, 10 patients (59%) underwent a retinectomy. Final VA improved (p=0.041) compared to the initial presentation.
In comparison with a control group of patients with PPV for the first RD and PPV with silicone oil for the second RD, matched for age and gender, the study group had a higher incidence of total RD and PVR in the first RD (p=0.016, 0.041, respectively). Furthermore, during the second operation, the study group experienced more retinectomy and PVR (P<0.01, P=0.03, respectively).
The final VA was worse in the study group compared to the control group (p=0.017).

Conclusions: Patients who underwent PPV with silicone oil for their first RD surgery presented with severe RD characteristics and poor VA. Their second RD was severe and required a retinectomy. However, their vision improved from their initial presentation. Therefore, in severe total RD or poor vision in the unaffected eye, PPV with silicone oil should be considered as the initial surgery. Further studies should investigate whether adding a band to the second surgery improves the prognosis.

A seven-year electroretinography follow-up of a patient with melanoma-associated retinopathy stabilized on pembrolizumab treatment.

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Purpose: Melanoma-associated retinopathy (MAR) is a rare, auto-immune paraneoplastic syndrome associated with metastatic melanoma. Over the last decade, patient survival has improved dramatically, mainly due to the development of immunotherapy. However, data on long-term MAR patient follow-up and response to modern standard-of-care treatment are lacking. This report presents a seven-year, multimodal follow-up of a young MAR patient treated with immune-checkpoint inhibitors (ICI).

Methods: A single-patient case report describing the clinical course and response to treatment of a MAR patient over a period of seven years. Response to treatment was assessed by repeated slit-lamp examinations, visual acuity (VA), fluorescein angiography, Humphrey 24-2 visual field (VF), optical coherence tomography (OCT), and full-field electroretinography (ERG) tests.

Results: A 46-year-old Israeli male with a history of cutaneous malignant melanoma presented with sudden onset of bilateral shimmering, flickering, and nyctalopia a year and a half after diagnosis. Shortly thereafter, new subcarinal metastasis was observed on Positron Emission Tomography–Computed Tomography (PET CT). Significantly reduced ERG a- and b-wave responses led to a diagnosis of MAR, later confirmed by high titers of autoantibodies against retinal bipolar cells. OCT showed a delayed macular thinning, particularly within the inner nuclear (INL) and inner plexiform (IPL) layers of the outer macular ring, with no substantial change in the outer retina. A treatment regimen combining intravenous immune globulin (IVIG), azathioprine, and prednisone allowed partial steroid tapering over the following 2.5 years, but showed substantial toxicity and lack of significant improvement on OCT and ERG. Pembrolizumab treatment was initiated following metastatic progression and resulted in stabilization of the patient's primary oncologic disease, as well as an increase in macular thickness and enhanced retinal function with an increase of over 60% in scotopic b-wave response over the following year.

Conclusions: MAR may be the first sign of systemic metastatic melanoma, thus warranting a high degree of clinical suspicion. While OCT and ERG showed mostly concordant results over the patients' follow-up, ERG proved to be a more sensitive tool for the early diagnosis of MAR. Early immunotherapy treatment should be considered in antibody-positive MAR patients.

Fabrication and characterization of 3D-printed, stem cell-derived tri-layered retinal implants

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Purpose: Advanced maculopathies, including age-related macular degeneration, lead to significant vision loss and lack effective treatments. This study aimed to engineer a 3-layer retina-like structure using 3D bioprinting that simulates the natural retinal architecture, potentially offering a new therapeutic avenue for retinal regeneration.

Methods: We utilized a sequential fabrication technique starting with 3D printing of a choroid-like vascular network using an extracellular matrix-derived hydrogel combined with human iPSCs-derived endothelial cells. Human retinal pigment epithelium (RPE) cells were then deposited to form a monolayer on the vascular print, followed by integration of photoreceptor cells on top of the RPE layer. This multistep process promoted the organization and maturation of each layer. Characterization included morphological assessment, marker expression analysis and functional evaluation.

Results: The 3D printed choroid-like layer successfully developed functional blood vessels lined with endothelial cells, which supported perfusion in vitro. Following RPE cell deposition, immunostaining confirmed the expression of key cellular RPE markers ZO1, BEST1, and RPE65, signifying effective maturation into a polarized monolayer. Transmission electron microscopy (TEM) illustrated definitive ultrastructural characteristics of RPE cells, such as pigmentation, apical microvilli, and desmosomes. Functionally, the RPE layer exhibited phagocytic activity, appropriate calcium signaling in response to ATP, and elevated trans-epithelial electrical resistance (TEER), indicative of a blood-retinal barrier mimicry. Subsequent deposition of photoreceptor cells on the matured RPE layer facilitated integration and expression of mature photoreceptor markers. This tri-layered construct sustained high cell viability and functionality throughout a 104-day observation period.

Conclusions: The biofabricated 3-layer retina-like structure closely mimics the human retinal architecture and demonstrates a high potential for contributing to effective treatments for retinal degenerative diseases. Each fabricated layer exhibited appropriate morphological characteristics and biological marker expression, demonstrating successful layer-specific differentiation and integration. This implant supports further investigations into its long-term viability and functional efficacy in vivo, with the prospect of future clinical applications.

Retinal Gene expression in response to Aβ results in a transcriptomic footprint similar to age-related macular degeneration

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Purpose: Amyloid-β (Aβ) assemblies, components of Alzheimer's disease brain plaques, are found in drusen, the hallmark lesions of age-related macular degeneration (AMD). We have previously shown the ability of Aβ42 assemblies to induce in vivo retinal toxicity and dysfunction following intravitreal administration in rats. Here, we aimed to better understand the acute impact of oligomeric and fibrillar Aβ42 assemblies on the neurosensory retina by identifying changes in gene expression in response to these assemblies.

Methods: In 2 parallel experimental cohorts, wild-type rats were injected with either fibrillar (FAβ42) or oligomeric (OAβ42) preparations (10µl). In each cohort, Aβ42 (n=4) or vehicle (n=4) was injected into the right eye of each rat. 4 days post-injection, rats were sacrificed and retinas were collected for transcriptome analysis using RNA-Seq. Pathway enrichment analysis was used to identify emerging pathways and differential expression of key proteins confirmed by immunostaining. To compare retinal transcriptional response to Aβ and AMD, we generated an ""AMD-related gene bank"" by integrating data from 6 AMD transcriptomic studies. This bank was then compared to our RNA-seq dataset.

Results: Administration of OAβ42 induced 52 differentially expressed genes (DEGs), of which 51 were upregulated. FAβ42 induced 13 DEGs, with 10 being upregulated. Pathway analysis revealed that OAβ42 primarily induced microglial activation, phagocytosis, engulfment, immune response regulation, and complement system involvement, whereas FAβ42 activated pathways involved in cholesterol synthesis and regulation, lipid metabolism and transport. Targeted examination of retinal DEGs in response to Aβ42 highlighted similarities to the transcriptional footprint of AMD. Notably, retinal cascades activated by OAβ42 differed from those triggered by FAβ42. OAβ42 primarily induced inflammation involving mediators reported to participate in AMD, such as CFH, S100A8, and S100A9. In contrast, FAβ42 was strongly linked to lipid metabolism via TXNIP, ABCA1, and APOE, which are known key effectors in AMD.

Conclusions: This study provides insights into the retinal pathogenicity of Aβ species, highlighting transcriptional and mechanistic pathways that arise in response to intravitreal administration of Aβ42. Our results align with previously reported Aβ related outcomes in the CNS. These data support the role of amyloid assemblies in AMD pathogenesis, as pathways related to retinal inflammation and lipid metabolism, which are implicated in AMD, are specifically activated by Aβ.

The presence of subretinal drusenoid deposits as a predictor of cardiovascular disease

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Background/purpose: The presence of subretinal drusenoid deposits (SDDs, also known as reticular pseudodrusen) in patients with age-related macular degeneration (AMD) appears to be correlated with cardiovascular disease (CVD) and may therefore serve as a useful tool for predicting certain forms of CVD. Here, we tested this hypothesis by examining whether patients with AMD with SDDs are more likely to have a cardiovascular-related condition and/or undergo a cardiovascular procedure.
Design: Retrospective cohort study.
Subjects: We included a total of 714 patients with AMD either with SDDs (with or without drusen; n=401 patients) or without SDDs (n=318 patients).

Methods: Patients who underwent spectral-domain optical coherence tomography (SD-OCT) were included, and the SD-OCT scans were annotated by two masked, experienced graders. We also extracted data from the patients' electronic medical records (EMRs), including patient demographics, the cardiovascular diagnoses, and CVD-related procedures based on ICD-9 codes.
Main outcome measures: Cardiovascular diagnoses and cardiovascular-related procedures performed in both patients' groups.

Results: Patients with SDDs were more likely to undergo a cardiovascular procedure compared to patients without SDDs, particularly angiocardiography of left heart structures (OR 1.9, 95% CI [1.17, 3.09]), left heart catheterization (OR 1.62, 95% CI [1.02, 2.59]), and either percutaneous transluminal coronary angioplasty (PTCA) or coronary atherectomy (OR 2.5, 95% CI [1.24, 5.03]).

Conclusions: These data suggest that the presence of SDDs in patients with AMD correlate with certain severe cardiovascular conditions. SDDs and CVD may share common pathogenic pathways, and potentially, therapeutic targets.

A Potential Role for Clusterin in the Pathogenesis of Age-Related Macular Degeneration (AMD)

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Purpose: We have previously characterized the proteomic profile in the aqueous humor (AH) from AMD patients. Notably, Clusterin/ApoJ (CLU) protein levels were increased in AH from eyes with non-neovascular AMD (n-nAMD) compared with eyes with neovascular AMD (nAMD). Here we aim to evaluate for potential involvement of CLU in the pathogenesis of n-nAMD and nAMD.

Methods: CLU potential effect in the context of nAMD was evaluated in mouse choroidal sprouting assay (CSA), and by intravitreal delivery of CLU in the mouse model of laser induced choroidal neovascularization (LI-CNV). Readouts included the choroidal sprouting area and the CNV area per isolectin staining of retinal pigmented epithelium-choroid flat mounts, respectively. CLU was also delivered intravitreally in the mouse model photic retinal injury to assess its potential role in n-nAMD. Readouts included electroretinogram (ERG) seven days post-injury. The effect of CLU on mononuclear cell migration was evaluated in human monocyte-derived macrophages as a measure of its potential involvement in retinal inflammation.

Results: A notable reduction in the mean (SD) choroidal sprouting area was observed when media from CLU-treated M2 macrophages was added to the culture (0.57 ±0.39), as compared with untreated M2 macrophages (1.09±0.79, n=11, p=0.024). Additionally, the CSA sprouting area was diminished following treatment with CLU (0.26±0.14 vs 0.46±0.21 n=12, p=0.0022). In the in vivo model of LI-CNV, the CNV area following intravitreal delivery of 10mg/ml CLU was smaller compared with the control mice (0.007±0.003 vs 012±0.006, p=0.033). In the model for photic retinal injury, ERG amplitudes were similar following CLU treatment (174.7±85.11) compared with controls (111.85±20.6, p=0.14). The migration assay indicated that CLU had no discernible impact on monocyte recruitment.

Conclusions: CLU, which is upregulated in n-nAMD eyes, can suppress choroidal sprouting ex-vivo, and diminish CNV growth in mice model of LI-CNV. This effect may be mediated in part by macrophages. The potential role of CLU as an endogenic anti angiogenic factor in AMD should be further evaluated.

The correlation of genetic risk scores with OCT biomarkers in AMD

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Purpose: 52 genetic variants associated with different biological pathways were associated with the risk for developing age related macular degeneration (AMD). Yet, there is limited data on their association with specific features of the disease. We aimed to evaluate for genotype-phenotype correlations among patients with AMD to gain further insights to the pathogenic pathways involved in the disease.

Methods: To assess genetic risk, we utilized a weighted genetic risk score method that quantifies the cumulative genetic predisposition of individuals by multiplying the number of risk alleles by the effect size measured as OR derived from the International AMD Genomic Consortium's analysis. The dataset consisted of 917 AMD patients (mean age±SD: 77±9 y) and 432 controls (mean age±SD: 71±8 y). A weighted score was calculated for 52 AMD risk variants (Global score), 19 complement-related variants (Complement score), 7 lipid-metabolism related variants (Lipid score), and 26 genetic variants related to other pathways (other pathways score). For 578 AMD patients with available optical coherence tomography (OCT) images, OCT-based phenotypic features were annotated, including presence of typical drusen, complete retinal pigmented epithelium and outer retinal atrophy (cRORA), sub-retinal drusenoid deposits (SDD) and hyperreflective foci (HRF). Correlation tests and Logistic regression were used to explore the relationship between disease features and genetic scores.

Results: Higher mean±SD complement score was present in AMD patients (0.67±0.05) compared with controls (0.27±0.06; P<0.0001), as well as a higher global score (AMD 1.45±0.11, Controls 0.65±0.07; P<0.0001). Drusen presence correlated with lipid score (r=0.09, P=0.02). cRORA and HRF displayed a positive correlation with ARMS2/HTRA1 (r=0.11, P=0.004; r=0.08, P=0.03 respectively). Logistic regression analysis indicated associations between cRORA and complement score (OR=1.25, 95%CI 1.05-1.50, P=0.01) and between HRF and ARMS2/HTRA1 (OR=1.53, 95%CI 1.03-2.27, P=0.04).

Conclusions: The study provides insights into genotype-OCT biomarkers relationships in AMD. Genetic risk variants for the disease are associated with specific OCT-based phenotypic features, as illustrated by cRORA's association with a high complement score or HRF's link with ARMS2/HTRA1. Such insight on the interplay between genetics and specific AMD characteristics, may have potential future implications for disease prediction and management.

Choroidal vasculature segmentation using SOTA AI model.

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Purpose:
The choroid nourishes the outer portion of the retina and is of key interest in numerous choroidal and retinal pathologies. The choroid consists of three layers of vessels: Choriocapillaris, Sattler and Haller vessels. Our study aimed to assess the use of an AI algorithm to automatically identify choroidal vasculature from OCT B-scan images.

Methods:
176 OCT B-scan images were collected from 176 eyes with AMD and pachychoroid-related diseases. The Yolo v8 SOTA model was used to segment the choroidal vessels from B-scan OCT scans. The data was allocated by a ratio of 8:1:1 for training, testing and validation.
The model's performance was internally validated, and the evaluation indicators included accuracy, specificity, and negative predictive value.

Results:
176 OCT B-scan images of 176 eyes were included in the analysis.
An AI algorithm was constructed, and accuracy, negative predictive value, positive predictive value, specificity, sensitivity, and area under the curve (AUC) will be announced at the convention.

Conclusion
In this study, we examined the performance of State Of The Art AI model - Yolo v8 architecture in identifying choroidal vasculature. Automatic segmentation of choroidal vasculature based on structural OCT scans will further improve our diagnosis and understanding of choridal and retinal pathologies.
This ability will set reference for further research on the role of choroidal vasculature.

Switching Anti-VEGF Therapy in Neovascular Age-Related Macular Degeneration: New Insights on Efficacy Using Automated Volumetric Retinal Fluid Analysis

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Purpose: To investigate outcomes of switching from bevacizumab (BCZ) to ranibizumab or aflibercept treatment, utilizing automated retinal fluid volume analysis as an accurate and quantitative measure for evaluating switching success.

Methods: Retrospective study at Tel Aviv Medical Center (TLVMC). Inclusion criteria: Eyes with insufficient response after ≥ 3 monthly BCZ injections that were switched to another anti-VEGF agent. After OCT image pre-processing, anonymized OCT scans were analyzed using the Notal OCT Analyzer (NOA), a validated AI-based OCT analysis algorithm, providing automated quantification of retinal fluid. “Early switchers” (≤5 bevacizumab) and “late switchers” (≥6 injections) were analyzed separately. Clinical data was recorded. OCT data included total retinal fluid volume (TRF, in nL), pigment epithelial detachment volume (PED; nL), and central subfield thickness (CST; µm). OCT measures were recorded at baseline, after BCZ treatment, and after 3 injections of 2nd line treatment. Wilcoxon signed-rank test was used to test for significance.

Results: 186 eyes of 186 patients were included. 143 (76.9%) were switched late. Mean age was 77.7±8.6 years, 105 (56.5%) were female. Among the early switch group, median TRF volume increased from 105nL (IQR 25-373) at baseline to 158nL (IQR 42-249) after BCZ and decreased to 20nL (0.5-99) after switch (p=0.00014). Median PED volume increased from 375nL (IQR 40-1203) at baseline to 401nL (101-1198) after BCZ and decreased to 269nL (47-984) after switch (p=0.00332). Among the late switch group, median TRF volume decreased from 221nL (54-580) at baseline to 87nL (23-261.7) after BCZ and to 5nL (0.00-35) after switch (p<0.0001). Similarly, the median PED volume decreased from 218 (50-632) at baseline to 174 (62-570) after BCZ and to 149 (0.00-479.80) after switch (p=0.0014). CST reduction was statistically significant in early switchers (p=0.0009) only. VA improvement was not statistically significant in either group (p=0.509 and p=0.927 for early and late switch, respectively).

Conclusions: Automated retinal fluid analysis provides accurate and valuable information on response to anti-VEGF treatment switch in nAMD. Eyes which were switched early showed a real non-response to BCZ, whereas late switchers were partial responders. In both groups switching led to significant reduction of disease activity, i.e. retinal fluid volumes. Further studies are warranted to characterize the subgroup that could benefit most from a switch and explore optimal switching regiments in nAMD.

Dyslipidemia in Age-related Macular Degeneration

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Purpose: We previously observed an upregulation of the HDL particles pathway in the aqueous humor (AH) of neovascular age-related macular degeneration (nAMD) patients compared to control and atrophic AMD (aAMD) patients. This upregulation is attributed to the increased expression of apoA1, apoA2, and PON1 proteins in this pathway. This finding aligns with existing literature on the lipid pathway involvement in AMD pathogenesis. In the current study, we aim to investigate the correlation between plasma HDL levels and HDL particles within the AH.

Methods: To evaluate the potential of HDL-associated proteins as biomarkers for AMD, we assigned a score to the upregulated proteins and performed a receiver operating characteristic (ROC) analysis for diagnostic accuracy. Subsequently, to assess potential associations between plasma HDL and HDL-associated proteins in the AH, we collected blood lipid profile data from patients with available AH proteomic information. The cohort comprised 36 nAMD patients (mean age 75±8.3 years, Female/Male=18/18), 22 aAMD patients (mean age 78.8±6.2 years, Female/Male=11/11), and 20 controls (mean age 76±8.9 years, Female/Male=12/8). Plasma HDL levels were first correlated with the overall protein scoring data and also analyzed for each upregulated proteins to identify potential relationships.

Results: The area under the curve (AUC) was computed by comparing aAMD, nAMD and controls to the scoring of HDL particles. When combining aAMD and nAMD into a single AMD group and comparing with controls, the AUC was 0.65. The AUC value was 0.567 when comparing controls with aAMD and increased to 0.714 when comparing controls with nAMD. In examining the correlation between plasma HDL levels and AH HDL particle scoring, a significant negative correlation was observed in nAMD patients (Pearson correlation R= -0.331, P=0.049). Each of the individual proteins displayed a significant negative correlation: ApoA1 (R= -0.405, P=0.014), ApoA2 (R= -0.360, P=0.031), and PON1 (R= -0.488, P=0.002). No correlation was identified in controls and in aAMD.

Conclusions: Preclinical studies have suggested that lipid dyshomeostasis likely contributes to the pathogenesis of AMD. The relationship between AMD and lipid homeostasis in human studies is not fully elucidated. Here we identified a negative correlation between AH proteome in nAMD patients and lipid homeostasis. These data emphasize the association between lipid homeostasis and AMD, suggesting that the dysregulations in lipid metabolism may differ depending on the specific subtype of the disease.

Xanthelasma Palpebrarum is Not Associated with Dyslipidemia or Cardiovascular Disease: A Case Control Study

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Purpose: Xanthelasma Palpebrarum (XP) is a benign condition involving yellowish periocular cutaneous lesions. Various studies have suggested associations with systemic disorders, mainly dyslipidemia and cardiovascular disease (CVD(, and XP patients are commonly referred for further evaluation. We aimed to inspect whether XP is associated with dyslipidemia or CVD in a large population.

Methods:Medical records of all individuals who were examined in a single medical screening institute between 2001-2020 were extracted, including data regarding ophthalmic evaluations, blood tests, and systemic diagnoses. Patients with XP in at least one eye were identified. Controls without XP were age and sex matched on a 10:1 ratio for robust statistical comparisons. Main outcome measure included the associations of XP with dyslipidemia and CVD.

Results: The database included 35,678 individuals, 24,287 males (69%), mean age 52.2±12.2 years. The study population included 203 XP patients (0.6%) and 2030 matched controls. The prevalence of dyslipidemia diagnosis and the usage rates of statins, fibrates, or other cholesterol-lowering medications was similar between the two groups. Lipid profiles were similar between the groups, including median total cholesterol levels, HDL, LDL, and triglyceride (187 controls vs. 192 XP, 48 controls vs. 47 XP, 120 controls vs. 125 XP, 111 controls vs. 105 XP, respectively, P>0.05 for all). The rate of CVD was similar as well (10% controls vs. 8.9%, XP P=0.56). The prevalences of related conditions including hypertension, Diabetes Mellitus, and history of cerebrovascular accident were similar between groups (24% controls vs. 23% XP, 14% controls vs. 10% XP, 1.3% controls vs. 1% XP, respectively P>0.05).

Conclusions: XP was not associated with dyslipidemia or CVD. This questions current clinical management concepts regarding the need to send all XP patients for blood tests or cardiovascular workups.

Punctal Atresia as a Clinical Indicator of Systemic Genetic Anomalies

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Purpose: To investigate a cohort of PA patients, examining the prevalence and types of associated syndromes.
Methods: A retrospective medical records review of all patients diagnosed with PA at the Children's Hospital of Philadelphia between 2009–2023 was conducted, analyzing medical histories and genetic testing results. Primary outcomes included the prevalence of systemic syndromes, while secondary outcomes focused on the variety of associated syndromes.

Results: Forty-four patients were included, of which 31 were male (70%) with a mean ± SD age 3.3 ± 3.3 years. Overall, 87 puncta in the study cohort were affected, and 26 cases (59%) were bilateral. Systemic abnormalities or genetic syndromes were identified in 19 patients (43%), with the most common being Ectodermal Dysplasia and Down syndrome. Additional rare syndromes were demonstrated. No significant association was found between systemic abnormalities and gender, bilaterality, or the number of puncta involved.

Conclusions: A high incidence of systemic syndromes (43%) was observed in the study cohort. In individuals with PA who also exhibit extraocular disease, systemic evaluation and genetic workup should be considered. Syndromic diagnoses identified in our cohort also include: Branchio-oto-renal syndrome, 22q11.2 deletion syndrome, 1q21.1 microdeletion syndrome, NF1, monosomy 4q and trisomy 6q, which represent novel associations. The lack of correlation between PA's phenotypic severity and systemic abnormalities highlights the need to obtain a comprehensive medical history and consider a systemic workup in PA patients.

Lacrimal Obstruction in Craniosynostosis: Anatomical and Genetic Risk Factors

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Purpose: To investigate whether patients with craniosynostosis exhibit higher rates of nasolacrimal duct obstruction (NLDO) and to explore potential risk factors.

Methods: Retrospective review including all craniosynostosis patients treated at both the Divisions of Ophthalmology and Plastic, Reconstructive and Oral Surgery at The Children's Hospital of Philadelphia between 2009-2020 were included. Synostosis characteristics, lacrimal disorders, and genetic data were collected. Main outcome measures were the rate of NLDO and associations with anatomical and syndromic/genetic risk factors.

Results: The total of 767 participants had a mean age of 2.8±3.8 years, 465 (60.6%) were males, 485 (63.2%) had no syndromic association; 631 (82.3%) had one major suture involved, 128 (17%) had involvement of 2 to 4 major sutures, and 429 (55.9%) underwent craniofacial surgery. Forty-eight (6.2%) patients had NLDO, which more prevalent in the genetic/syndromic group (11.0% vs. 3.5%, respectively, $P < 0.001$), with the highest prevalence observed in patients with Apert syndrome (n=4, 30.8%). The genetic variants most associated with NLDO were EFNB1 (n=1, 100%) and FGFR2 (n=6, 19.4%). There was no association between NLDO and the number or types of sutures involved or a history of craniofacial surgery.

Conclusion: NLDO is more common in patients with craniosynostosis compared to the general population. Having a putative syndrome or a putative genetic variant as well as female sex were risk factors for NLDO. Ophthalmic evaluations for all craniosynostosis patients and careful assessments of any symptoms of tearing are recommended.

Characterization Of The Ocular Microbiome In Anophthalmic Patient

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Background: The ocular microbiome, encompassing a myriad of microbial communities residing on the ocular surface, is pivotal in upholding ocular health and equilibrium. Variations in the composition of the ocular microbiome are known to occur among individuals and were recently examined in patients with ocular prostheses. This study aims to compare the ocular microbiome between individuals with healthy eyes and ocular prosthesis socket in our community.

Methods: The study cohort included 13 patients with an ocular prosthesis, of those only 5 samples were successfully analyzed. The fellow eye served as healthy controls. In compliance with the Helsinki Declaration and following Institutional Review Board approval, study participants signed an informed consent. Participants completed a comprehensive medical questionnaire regarding their systemic and ophthalmic medical history and the condition of their ocular prosthesis. Conjunctival swabs were taken from the conjunctival fornix of both eyes. Sampling was performed using a sterile cotton applicator. A 16SrRNA sequencing kit was used to characterize the microbiome composition.

Results: Addressing the challenges posed by limited sample sizes, the analysis of the microbiome profile uncovered a diverse array of bacteria with restricted expression. Prevotella 9, Cutibacterium, and Faecalibacterium had increased expression in the control eye. The prosthesis eye displayed an increased expression of Pseudomonas, Alcaligenes, and Fusobacterium, while also having more diverse bacterial distribution in general.

Conclusion: Significant differences in microbiome composition exist between the conjunctival microbiome of control and prosthetic eyes. Enrolling a larger patient cohort could aid in characterizing the specific microbial communities present and assist in developing customized treatments based on bacterial sensitivities. Understanding the microbial dynamics related to ocular prostheses could lead to personalized treatment strategies that enhance the quality of life for individuals using ocular prostheses.

Orbital Development in Children with Retinoblastoma: An Imaging-based Study

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Purpose: To examine whether children treated for Retinoblastoma (Rb) have impaired orbital development.

Methods: A retrospective case series was performed among children with Rb treated at a single medical center from 2004-2020. Orbital volumes and measurements were assessed by 3-dimensional image processing software. The main outcome measures were differences in orbital growth between Rb and non-Rb eyes assessed at last follow-up.

Results: Among 44 patients included (mean age 16.09±18.01 months), a positive correlation between age and orbital volume was observed only in in the uninvolved, healthy eyes (P=0.03). In unilateral cases, orbital growth in the horizontal, vertical, and depth planes was smaller on the affected side compared to the healthy eyes (P<0.05). Orbits that underwent enucleation showed decreased growth over time compared to those treated conservatively (P=0.017).

Conclusions: Orbital growth rate is slower in the orbits of children treated for Rb compared to healthy orbits. Enucleation negatively affects orbital growth.

A Novel Semi-Automated MRI-Based Method for Orbital Volume and Contour Analysis Compared with CT-Based Dimensions

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Purpose: The orbital cavity's complex architecture requires accurate measurement for managing eye and orbital issues. Most measurements use CT scans, but MRI is useful for soft tissue, especially in pediatric cases. This study introduces a new semi-automated MRI method for visualizing orbital shape and size.

Methods: This retrospective cohort study employed manual segmentation and three-dimensional (3D) image processing software to determine orbital dimensions, encompassing volume, horizontal and vertical lengths, and depth, from both CT and MRI imaging modalities. Participants comprised patients with at least one normal orbit who underwent both CT and MRI scans at a single center between 2015 and 2023. The primary objective was to assess differences in orbital measurements between MRI and CT scans.

Results: Thirty-one patients (mean age 47.7±23.8 years, 21 [67.7%]) females, were included.
The mean differences in delta values between orbital measurements on CT vs. MRI were: volume 0.03±2.01 ml, horizontal length 0.53±2.12 mm, vertical length, 0.36±2.53 mm, and depth 0.97±3.90 mm. The CT and. MRI orbital measurements were strongly correlated: volume ($r=0.92$, $P<0.001$), horizontal length ($r=0.65$, $P<0.001$), vertical length ($r=0.57$, $P=0.001$), and depth ($r=0.46$, $P=0.009$). The mean values of all measurements were similar on the paired-samples t-test: $P=0.9$ for volume (30.86±5.04 ml on CT and 30.88±4.92 ml on MRI), $P=0.2$ for horizontal length, $P=0.4$ for vertical length, and $P=0.2$ for depth.

Conclusions: We present an innovative semi-automated method capable of calculating orbital volume and demonstrating orbital contour by MRI validated against the gold standard CT-based measurements. This method can serve as a valuable tool for evaluating diverse orbital processes.

Nasal and temporal intraconal orbital fat densities differ on computerized tomographic scans of normal orbits

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Purpose: The anatomy and function of different areas within the intraconal fat remain poorly understood. A potential difference between nasal and temporal orbital fat densities in normal eyes may assist clinicians and radiologists in more accurately interpreting computerized tomographic (CT) scans and making more informed diagnostic and therapeutic decisions for patients with orbital pathologies.

Methods: Data from randomly selected patients who underwent orbital CT scans at Sheba Medical Center in 2022 were analyzed. Patients with abnormal imaging findings in either orbit were excluded. Intraconal orbital fat density was measured in six nasal and temporal sites by means of Hounsfield units (HU).

Results: The study included 54 patients (mean age 45.3±25.5 years, 29 [54%] females) who were scanned for ophthalmologic etiologies unrelated to the orbit. Non-contrast-enhanced (NCE)-CT scans were available for 36 patients (67%), CE-CT scans for 31 patients (57%), and both CE and NCE scans for 13 patients. HU values were significantly higher in the nasal orbit compared to the temporal orbit on both NCE-CT (-75.8±7.5 nasal vs. -78.1±8.4 temporal, $p < 0.001$) and CE-CT (-72.7±6.7 nasal vs. -74.6±8.6 temporal, $p = 0.02$). Age, sex, and laterality had no effect on the HU values.

Conclusions: The density of nasal intraconal fat is higher compared to temporal intraconal fat, as observed on both CE and NCE-CT scans of normal eyes. These results suggest the presence of anatomical differences between these compartments and could have significant clinical implications in the diagnosis of various orbital pathologies.

Computer Aided Diagnosis of Eyelid skin tumors Using Machine Learning

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Purpose: To develop an automated, new framework based on machine learning to diagnose malignant eyelid skin tumors.

Methods: This study utilized eyelid lesion images from Sheba Medical Center, a large tertiary center in Israel. Before model training, we pre-trained our models on the ISIC 2019 dataset consisting of 25,332 images. The proprietary eyelid dataset was then used for fine-tuning. The dataset contained multiple images per patient, aiming to classify malignant lesions in comparison to benign counterparts.

Results: The analyzed dataset consisted of images representing both benign and malignant eyelid lesions. For the benign category, a total of 373 images were sourced. In comparison, the malignant category 186 images. Based on the accuracy values, the model with 3 epochs and a learning rate of 0.0001 exhibited the best performance, achieving an accuracy of 0.748 with a standard deviation of 0.034. At sensitivity 69% the model has a corresponding specificity of 82%. To further understand the decision-making process of our model, we employed heatmap visualization techniques, specifically Gradient-weighted Class Activation Mapping.

Discussion: This study introduces, for the first time, a dependable model-aided diagnostic technology for assessing eyelid skin lesions. The model demonstrated accuracy comparable to human evaluation, effectively determining whether a lesion raises a high suspicion of malignancy or is benign. Such a model has the potential to alleviate the burden on the healthcare system, particularly benefiting rural areas, and enhancing the efficiency of clinicians and the overall healthcare."

Should we ask AI for approval for blepharoplasty surgery?

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Background:
Blepharoplasty is a surgical procedure used to correct redundant and lax skin of the eyelids (dermatochalasis) and preaponeurotic fat herniation, which can result in either functional visual symptoms or cosmetic concerns. Blepharoplasty of the upper eyelid accounts for the majority of blepharoplasty surgeries and has increased in recent years. Currently, measurements to indicate the need for blepharoplasty are susceptible to human errors. all of which, result in an overload of requests that need to be reviewed for eligibility for surgery.
Aim:
To evaluate the use of an AI model for grading indications for blepharoplasty based on facial photographs.

Methods:
200 Facial images of patients were pre-processed and analyzed to identify the anatomic structures of the ocular area.
Image preprocessing was done to account for image resolution, lighting, patient distance from the camera, and different cameras. An AI model was used to segment ocular landmarks: sclera, iris, eyebrows, eyelids, and light reflex. The data was allocated in a ratio of 8:1:1 for training, validation, and testing.
The model's performance was internally validated, and the evaluation indicators included accuracy, specificity, and negative predictive value.

Results:
Overall, 400 eyes (200 patients) were included in the study. Anatomical structures were identified, as well as margin reflex distance (MRD) was calculated from all images regardless of the distance from which they were taken.
An AI algorithm was constructed, and accuracy, negative predictive value, positive predictive value, specificity,
sensitivity, and area under the curve (AUC) will be calculated and presented at the convention.

Conclusion:
Grading of facial images for approval of blepharoplasty surgery can be done using AI. AI models are capable of measuring ocular landmarks reliably regardless of the resolution, distance, or camera used.

The retinal pathways triggered by Amyloid-β42 30 days after exposure are related to AMD pathological processes

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Purpose: Age-related macular degeneration (AMD) has a complex unsolved pathophysiology. Several pathways such as lipid metabolism, activation of the complement system, oxidative stress response and mitochondrial dysfunction were highlighted as essential pathways in AMD, yet little is known about the triggers for these events. Amyloid β (Aβ), a family of polypeptides prone to self-assemble into toxic aggregates is a significant component of drusen, thus implicated in the pathophysiology of AMD. We have previously shown that Aβ42 is retinotoxic and that oligomeric assemblies exerted the predominant pathogenicity. Assuming that Aβ42 may initiate long-term pathological retinal cascades, we conducted a transcriptomic analysis to identify mechanisms of retinal changes 30 days post Aβ exposure.

Methods: Adult female Sprague-Dawley rats were employed. In each rat the right eye was intravitreally injected with 10µl fibrillar Aβ42, oligomeric Aβ42 or their corresponding vehicle (n=4 for each group). The neurosensory retina was explanted 30 days after treatment and high-quality RNA samples were extracted for transcriptome analysis using RNA-sequencing (RNA-seq). A Gene Ontology analysis was conducted in IPA and in R software using DOSE and enrichplot (IPA, Qiagen Inc., R Core Team, Vienna, Austria).

Results: At 30 days following treatment, 29 genes were differentially expressed in experimental retinas treated with Aβ42 oligomers versus controls and 22 genes were differentially expressed after fibrillar Aβ42 treatment. The most prominent upregulated genes in the group treated with oligomers were Tlr2, Klf2 and CFH, known for their involvement in neuroinflammation induced by Aβ. Additionally, Chac1, Atf5, Mthfd2 and Trib3, that are important for maintaining mitochondrial activity and preventing apoptosis were downregulated in response to oligomers. In retinas treated with fibrils, cxcl10, a part of a cytokine complex known to be upregulated in Aβ pathology, and a suppressor of mitochondrial respiration and cellular metabolism was significantly upregulated.

Conclusion: Our data highlight two major pathways activated by Aβ42 in the retina at a chronic stage, including an inflammatory response and mitochondrial dysfunction leading to apoptosis. These results shed light on the retinal response to Aβ42 and can deepen our understanding of Aβ42 involvement in the pathogenesis of AMD.

Ranibizumab clearance through the aqueous outflow pathway system in a rat model

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Background: The etiology of ocular hypertension and glaucoma following intravitreal administration of anti-VEGF agents is yet unknown. One of the suggested causes is the mechanical aggregation and obstruction theory.

Purpose: Our objective was to examine whether Ranibizumab molecules aggregate in the aqueous outflow pathways through the iridocorneal angle following an intravitreal injection in a rat model.

Methods: Choroidal neovascular lesions (CNV) were induced in the right eye of 12 brown Norway rats, using indirect laser ophthalmoscope. 3µl Intravitreal injection of Ranibizumab (0.5mg/0.05ml) was performed 3 days than after. The rats were euthanized at predetermine times: At zero, 3, 6, 24, & 48 hours after injection with immediate enucleation for Immunohistochemical antibodies immunostaining and image analysis.

Results: Positive and negative control groups verified the validity of the antibodies used. At the iridocorneal angle the peak of immunostaining signal of Ranibizumab was immediately after injection with a gradual decline 6 hours after injection. 24 hours after the injection signal was reduced by 4-fold. 48 hours after injection the immunostaining signal was negligible, confirming complete clearance of Ranibizumab from the outflow tracts in the iridocorneal angle.

Conclusions: The presence of Ranibizumab after an intravitreal injection in the iridocorneal angle in a designated rat model demonstrated no process of aggregation or obstruction as seen with complete clearance by immunofluorescence analysis 48 hours after injection.

A novel delivery device for scleral cross-linking for the treatment of myopia

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Purpose: To investigate the efficacy of a novel delivery device system for scleral cross-linking in live rabbit eyes.

Methods: Indocyanine green (ICG) was injected into the sclera of eight rabbits. ICG distribution was assessed by histology analysis. Three rabbits received a scleral injection of Riboflavin A (clinical formulation: isotonic solution: 0.1%Riboflavin, 20% Dextran 500) at two locations (superior-temporal and inferior-nasal) followed by UVA irradiation for 30 minutes. Eyes were cut open along the corneoscleral margin to remove contents of the anterior and posterior ocular segments. The sclera was rinsed clean with 0.9% normal saline. Scleral pieces (3mmx3mm) were incubated with Collagenase A (3.48mg/ml, 1677U/ml) for 16 hours to determine the efficacy of scleral cross-linking.

Results: ICG was detected across the sclera, reaching the optic nerve head following injection of 0.15 ml ICG. No dye was detected in the retina, lens, vitreous, or anterior segment. Flat-mount analysis revealed a coverage area of >75% of the sclera. Scleral pieces derived from regions in proximity to the injection site, covering 33% of the sclera, were resistant to collagenase-A treatment, suggesting effective collagen cross-linking.

Conclusions: The novel scleral delivery device may enable the injection of cross-linking agents into the sclera, reaching the posterior pole. Future studies will assess the system's ability to stiffen the sclera and prevent axial length growth.

Exosomes derived from mesenchymal stem cells attenuate Amyloid β toxicity in rat retina

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Purpose: Age-related macular degeneration (AMD) poses a complex pathogenesis with unclear underlying molecular mechanisms. Previous studies have highlighted the presence of Amyloid β (Aβ) in drusen, suggesting the involvement of this group of neurotoxic peptides in the development of the disease. We previously demonstrated clear retinal pathogenicity of various Aβ species in rats. Recently, exosomes derived from mesenchymal stem cells sourced from adipose tissue (AT-MSC-Exosomes) have shown promise in neurodegenerative state such as Alzheimer's disease given their ability to modulate inflammation and provide trophic support. Such an approach could be beneficial in retinal pathology related to Aβ. This study explored the efficacy of AT-MSC-Exosomes in ameliorating Aβ-induced retinotoxicity.

Methods: Wild-type rats were treated with intravitreal injections (10µl) of AT-MSC-Exosomes in one eye 5 days prior to injection of fibrillar Aβ42 assemblies into both eyes. Retinal function was assessed by electroretinography (ERG) at baseline, following AT-MSC-Exosome injection, and through 28 days after Aβ administration. ARPE-19 cells were treated with AT-MSC-Exosomes for 1hr before exposure to fibrillar Aβ42 for 18hrs. Cell viability was determined by the XTT proliferation assay. Fluorescent-labelling of AT-MSC-Exosomes was employed to track their cellular uptake under conditions of amyloid-related toxicity.

Results: ERG responses in rat eyes treated with AT-MSC-Exosomes prior to administration of toxic fibrillar Aβ42 assemblies were nearly intact compared to controls. The amplitudes of the ERG a-wave and b-wave were close to normal, while those obtained from control eyes treated with Aβ42 assemblies alone showed significant reductions. No retinal damage was observed in eyes treated solely with the AT-MSC-Exosomes. Moreover, AT-MSC-Exosomes protected ARPE-19 cells from Aβ42-induced toxicity. Compared with controls, AT-MSC-Exosomes exhibited increased migration in cell cultures which were exposed to the toxic Aβ42 fibrils.

Conclusion: AT-MSC-Exosomes demonstrated robust protection against Aβ-mediated retinotoxicity in vivo and in vitro. Successful migration and uptake of exosomes was observed in the context of amyloid-mediated injury. Such insights hint at the potential relevance of AT-MSC-Exosomes in treatment of Aβ-related retinal pathology. This study highlights a promising therapeutic avenue for AMD, leveraging the neuroprotective properties of AT-MSC-Exosomes.

Light-dark transition test in wild type mice and animals with advanced retinal degeneration

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Purpose: Rodent models of retinal degenerative diseases are an important tool for developing gene and cell-based therapies. The evaluation of visual function is pivotal to track degeneration and to determine therapeutic efficacy. Electroretinography (ERG) and the optokinetic response are commonly utilized in rodents to assess visual function. However, their efficacy diminishes notably in advanced stages of degeneration due to a “flooring effect”, associated with a limited population of functional photoreceptors. The light-dark transition test (LDTT) is advantageous as it directly assesses visual function of subject mice without relying on trained behaviors or indirect indicators, capitalizing on their innate aversion to brightly illuminated areas. Using this test, we compared visual function in wild type (WT) and Rd10 mice with advanced retinal degeneration.

Methods: The LDTT was performed in a home-built apparatus comprised of a dark black chamber (21x21x31 cm) and a brightly illuminated white chamber (21x21x25 cm) with a small (5x3 cm) gate between them. The light chamber was illuminated by LED lights with the intensity optimized to 11000 lux homogenously distributed across the floor of this chamber. Mice were initially placed in the dark chamber but were able to move freely between the two compartments for 10 minutes after a short adjustment period, with their movement tracked by video. Light avoidance, number of transitions and distance covered in the light chamber were analyzed by EthoVisionXTã software. WT mice were tested at 6, 10 and 13 months old (n=9). Rd10 mice were tested at 9 months old (n=6).

Results: WT mice avoided the light chamber and spent a mean of 81% (SEM ±2.1, n=9) of the time in the dark chamber. Rd10 mice didn’t show a clear preference for either chamber and spent a mean of 58% (SEM±2.8, n=6) of the time in the dark chamber. WT mice crossed between compartments significantly less (18±2.9 times) compared to Rd10 mice (41±3 times). Furthermore, WT mice covered a significantly smaller distance (644.1cm±99.1) compared to Rd10 mice (1535.1cm ± 92.9) in the light chamber.

Conclusions: These results suggest the LDTT can detect visual function changes due to photoreceptor loss. The outcomes are determined primarily by light perception, offering a sensitive measure of visual function. This test may be particularly useful in rodents with advanced retinal degeneration in which ERG and the optokinetic response are non-detectable.

Cross-linked hyaluronic acid enhances tear film concentrations of topical antibiotics in canine eyes

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Purpose: To compare tear film concentrations of cefazolin and chloramphenicol formulated with two different excipients.

Methods: Ten ophthalmologically healthy dogs were used in the study. Cefazolin and chloramphenicol were compounded as 5% and 0.5% solutions respectively, using both 1.4% polyvinyl alcohol (PVA) and 0.75% cross-linked hyaluronic acid (XHA). On two separate occasions, one month apart, dogs received cefazolin-PVA or chloramphenicol-PVA in one randomly selected eye, and the same antibiotic diluted in XHA in the contralateral eye. Tear fluid was collected from each eye using 2-µl capillary tubes at 0, 1, 5, 10, 15, 30, 60, 120, 240, 360 and 480 min following eyedrop administration. Tear concentrations of cefazolin and chloramphenicol were measured using UV-Vis spectrophotometry.

Results: Mean tear film concentrations of cefazolin and chloramphenicol were significantly higher with XHA compared to PVA at all time points except for 60 and 120 min for cefazolin ($P \leq 0.046$). With both formulations tear film kinetics were somewhat biphasic, with drug levels decreasing between 0-120 min, then slightly increasing between 120-360 min before declining again until the end of the experiment (480 min). The area under the time-concentration curve (AUC0-480) was significantly greater with XHA vs. PVA formulations ($P \leq 0.002$), being, on average, 2.7 greater for cefazolin and 4.1 greater for chloramphenicol.

Conclusion: XHA significantly increased tear film concentrations of cefazolin and chloramphenicol compared with PVA, a finding that might help reduce dosing frequency and improve clinical outcomes in patients with bacterial keratitis. Future studies could assess XHA formulations in diseased eyes, and determine the clinical breakpoints against common bacterial pathogens.

Pathological Ultrastructural Alterations of Optic Nerve Axons in Cobalt Toxicity: Correlation with MRI Imaging Changes

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Introduction: cobalt is an essential element to our body, however, at high level it can be toxic. Cobalt toxicity is known to induce visual dysfunction with unclear pathophysiology. Clinical reports indicating retinopathy and optic nerve neuropathy has been reported. The aim of this study was to explore the pathophysiology of cobalt toxicity on the optic nerve using manganese enhanced magnetic resonance imaging (MEMRI) and correlate it to ultrastructural changes on transmission electron microscopy (TEM).

Methods: 5 wild type mice (WT, C5Bl6) were injected with cobalt chloride intraperitoneally (IP) daily for 2 months while other 5 WT mice were injected with saline and served as a control. Mice underwent MEMRI imaging after two months of daily administration of cobalt chloride then were euthanized. Following euthanization, eyes were enucleated and optic nerve tissue underwent histological, immunohistochemical, TEM, and molecular analysis.

Results: in the optic nerves, an increased manganese signal on MEMRI was noted with increased microglial and astrocytic activation on immunohistochemical analysis. Signs of optic nerve damage and neurodegeneration on TEM such as axonal enlargement and demyelination, swollen axonal and astrocytic mitochondria, condensed electron opaque axoplasm and axons filled with cellular debris were all highly evident in comparison to control mice.

Conclusion: chronic cobalt toxicity caused heightened inflammatory response mainly by microglial cells and profound neurodegeneration, characterized by demyelination, increased glial activation, and mitochondrial failure similar to the pathophysiology of Leber hereditary optic neuropathy (LHON).

The role of the CCR1 receptor during retinal degeneration

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Purpose: Inflammation was implicated in the progression of retinal degeneration. Macrophage's recruitment, partly through the CCR1 receptor, was also associated with the process, and we have recently showed that CCR1 activation in retinal Muller cells plays a role in photoreceptor death in mouse models of retinal injury. Here we aim to further investigate the role of CCR1 in retinal degeneration using Ccr1 genetic deletion and CCR1 inhibition strategies.

Methods: Retinal structure of Crb1rd8/Ccr1-/- mice was compared with Crb1rd8 mice and with wild type mice at the age of 15 months. Readouts included grading of abnormal structure in fundus autofluorescence (FAF) imaging and retinal histological analysis. Retinal inflammation was assessed using real-time quantitative PCR (qPCR). Pde6brd10/Ccr1-/- mice were also generated, and retinal function was compared with Pde6brd10 mice, at 3, 4, and 5 weeks, using electroretinography (ERG). Additionally, CCR1-specific antagonists BX471 (50 mg/kg) and CCX354 (100 mg/kg) or vehicle (40 % cyclodextrin) were administrated to Pde6brd10 mice from P21 to P24, every 8 hours via subcutaneous injection followed by ERG recording.

Results: Grading of FAF images in wild type mice, Crb1rd8 mice, and Crb1rd8/Ccr1-/- mice (n=6 per group), revealed that the deletion of Ccr1 is associated with a decrease of fundus lesions, indicated by the presence of multiple bright spots in the retina. Histological analysis demonstrated increased retinal thickness, an improved retinal structure, and the absence of recruited macrophages in Crb1rd8/Ccr1-/- mice. qPCR analysis of Cxcl10, Cxcl1, Ccl2 and F4/80 mRNA levels showed decreased expression in Crb1rd8/Ccr1-/- mice compared with Crb1rd8 mice (n=6, 0.10; 0.28; 0.09; 0.28-fold change compared with 15m, respectively; and 0.16; 0.016; 0.35-fold change compared with 18m, respectively). Deletion of Ccr1 in Pde6brd10 mice, was associated with improved retinal function compared with Pde6brd10 mice per ERG (n=6, 1.26-fold change). ERG showed that CCR1 blockage with BX471 and CCX354 in Pde6brd10 mice, also delayed the course of photoreceptor loss compared with vehicle-treated mice (n=6, 2.13-fold change and n=5, 1.42-fold change, respectively).

Conclusion: Ccr1 deletion is associated with diminished retinal injury in rd10 and rd8 models of retinal degeneration. Pharmacologic inhibition of CCR1 conferred a protective effect in the rd10 model. Together, these findings suggest that CCR1 may serve as a novel therapeutic target for retinal degeneration.

in-vitro Differentiation and Further in-vivo Maturation of Retinal Precursor Cells Derived from Human Embryonic Stem Cells

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Purpose: Cell-based therapy may potentially support/replace degenerating host photoreceptor cells (PRs). In this study, Human Embryonic Stem Cells (hESCs) derived-retinal precursors cells (RPCs) were characterized in-vitro. Survival and further maturation following subretinal (SR) transplantation in immunodeficient mice was assessed in-vivo.

Methods: The HADC102 hESCs line was engineered to express GFP under control of the endogenous CRX promoter. hESC-CRX-GFP cells were cultured for 12-16 weeks (w) with neurotrophic factors, while monitoring GFP (CRX) expression over time. In-vitro characterization using immunocytochemistry (ICC), RNA sequencing (RNA-seq) and flow cytometry (FACS) analyses were performed. At the age of 12w the RPCs were transplanted into the SR space of immunodeficient mice. In-vivo examinations included Micron III fundoscopy for GFP visualization and OCT imaging. Engraftment and expression of retinal markers were assessed histologically and by immunohistochemistry (IHC) at 4, 8, 12, 16, 20, 22 and 55w post-op.

Results: ICC and RNA-seq analysis of hESCs-derived RPCs after 12w of in-vitro differentiation revealed a retinal gene expression signature including presence of CRX, RCVRN, ELAVL3, TRPM1, among others. FACS analysis showed that after 16w, over 45% of the RPCs were GFP:CRX-positive. In-vivo Micron III fundoscopy revealed GFP expression persisting up to 55w post-transplantation, indicating long-term survival of transplanted RPCs, while OCT scans demonstrated presence of SR grafts without tumor formation. IHC revealed transplanted RPCs exhibited a preference for self-organization into rosette structures, demonstrated morphology of PRs including formation of outer segments, and expressed PR-specific markers. In some cases, the PRs were surrounded by and made contact with cells expressing retinal bipolar cells (RBCs) markers. Importantly, the expression of PR markers was observed exclusively when the transplanted RPCs were located in the SR space. This indicates the importance of a proper microenvironment for the differentiation of hESC-derived RPCs into PRs in vivo.

Conclusions: Following 12w of in-vitro culturing, a substantial percentage of hESC-derived RPCs express retinal genes. Transplanted RPCs exhibit long-term survival in-vivo without evidence of tumor formation or retinal detachment. When located in the SR space, RPCs form rosette-like structures and mature into PRs and RBCs.

Investigating the Bmp4 pathway regulation effect on Photoreceptors' neurite outgrowth in in-vitro and ex-vivo models

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Purpose:
Pluripotent-derived photoreceptor transplants are a promising treatment for outer retinal degenerative diseases, which are manifested by the loss of photoreceptor cells but with relatively preserved other retinal layers. A significant challenge, however, is the ability of the transplanted cells to integrate with the host retina through the extension of neurites and synaptogenesis. The goal of this study is to investigate the effect of various molecules and on the ability of rat photoreceptor precursors (rPRP) to extend neurites and understanding the mechanisms which regulate these processes. We focused on RhoA, its related kinase (ROCK), Taurine (Tau) and glial cells media on neurite extension (RCM).

Methods:
rPRP cells derived from neonatal SD rats were cultured on PLL/laminin coated plates. The cultures were treated with ara-C to inhibit glial cells proliferation, followed by treatment with various molecules. After three days, the cells were stained for the PRP marker CRX and actin and the length of their extensions was measured. To characterize signal pathways involved in neurite extension, RNA-seq analysis was performed on cell cultures treated with ROCK inhibitor (Y27632) and compared to a control group. The results were validated by qPCR of selected genes and was tested conditioned media (CM) and Tau with the same methods.

Furthermore, we established an ex-vivo model in which rPRP cells were seeded on a degenerated retina, to investigate neurite extension toward the inner retinal cells.
Results:
Following ROCKi treatment, CRX positive cells exhibited dose dependent increase in cell percentage with processes and increase in neurites length Glial condition media and Tau had a weaker effect on the cells. RNA-seq analysis identified several upregulated pathways. qPCR analysis for these 3 treatments showed an upregulation of Bmp4 of more than 2 FC. Preliminary results of Bmp4 treatment exhibited neurite extension and retraction by inhibition of this pathway. Finally, rPRP cells seeded on the explant model with the mentioned treatments extended neurites towards the retina bipolar cells after 24h.

Conclusions:
Findings presented here provide a foundation for improving neurite extension and synapse formation between the host retina and transplanted cells, addressing one of the major challenges in cell replacement-based vision restoration.

Correction of the Achromatopsia-causing splice defect created by the deep intronic CNGB3- c.1663-1205G>A mutation using an antisense oligonucleotide

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Purpose: Achromatopsia (ACHM) is an autosomal recessive disease with a prevalence of 1:31,118 in the Israeli population. The disease is characterized by lack of cone function leading to very low visual acuity, absence of color vision, photophobia and nystagmus. The disease is heterogeneous and mutations in CNGB3 are the most common cause of ACHM worldwide. We previously reported of a deep intronic CNGB3 variant as one of the most common CNGB3 mutations in the Israeli and the European populations. This mutation creates a pseudoexon which leads to a premature stop codon. Antisense oligonucleotide (ASO) therapy is an emerging therapeutical modality that is being intensively explored in recent years, including the establishment of clinical trials. In the current study we aimed to identify an efficient ASO for correcting the splicing defect of the deep intronic CNGB3- c.1663-1205G>A mutation.

Methods: ASOs for the c.1663-1205G>A mutation were designed based on temperature, length, secondary RNA structure, GC ratio etc. Following in-vitro transfection of HeLa and 661W cells with a plasmid expressing the mutant sequence, we studied the effect and efficacy of the ASOs in correcting the splicing defect.

Results: Four possible ASO sequences were identified by applying the parameters, one of which, termed ASO-CNGB3-1205, received by far the highest score. Splicing assay analysis of the CNGB3- c.1663-1205G>A mutation in HeLa and 661W cells revealed the generation of a pseudoexon in 52% of transcripts in both cell lines. Following the application of ASO-CNGB3-1205, 99% and 88% normal transcripts were evident in HeLa and 661W cells, respectively.

Conclusions: We developed an ASO for the deep intronic CNGB3- c.1663-1205G>A mutation which is efficient in the studied cell lines. Our next step is to study the efficacy of ASO-CNGB3-1205 in the mouse retina.

iPSC-derived RPE models for RP11 disease modeling and treatment development

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Purpose: Mutations in the pre-mRNA processing factor 31 (PRPF31) lead to autosomal dominant retinitis pigmentosa (RP) 11. We aim to study the role of PRPF31 in patient-derived retinal pigment epithelium (RPE) models and use these models to develop a treatment for RP11.

Methods: Induced pluripotent stem cells (iPSC)-derived RPE models were established from skin biopsies of two RP11 patients and a healthy subject. RPE cell phenotype was assessed by immunofluorescence analysis using antibodies directed against Ezrin (a microvilli marker), ARL13B (cilia marker), and MERTK (an RPE apical receptor mediating photoreceptor phagocytosis). A novel high-throughput drug screening (HTS) platform was established to identify approved/investigational drugs that increase the expression of the PRPF31 WT allele. Selected drugs were tested for toxicity and phenotype reversal in the patient-derived RPE models.

Results: Normal PRPF31 protein levels were observed in RP11 patient-derived skin fibroblasts. By contrast, PRPF31 mRNA and protein levels were two-fold lower in patients' RPE cells compared with control. Aberrant cell polarity, cilia morphology, and mitochondria function were observed in the RP11-RPE models. Treatment with drug #C15, identified by HTS, elevated PRPF31 mRNA and protein levels in RP11-RPE cells and improved mitochondria function and cilia morphology.

Conclusions: RPE models were successfully established for a healthy donor and two RP11 patients. These models suggest that PRPF31 splicing dysfunction affects cell polarity, cilia morphology, and mitochondrial respiration. Moreover, our combined approach of HTS and patient-derived RPE models identified a novel potential drug-based therapy for RP11.

A new rat model for retinal degeneration: The GCaMP6f+\- RCS-\- Rat

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Purpose: Retinal degeneration (RD) is one of the most common causes of blindness in the western world. Our research aims at developing an animal model which enables the optical recording of retinal ganglion cells (RGCs) activity which can significantly enhance the functional evaluation of treatment modalities aimed at vision restoration in these patients.

Methods: The development of the novel rat model is based on a new breed in which retinal degenerated Royal College of Surgeons (RCS) rats is crossbred with the transgenic line LE-Tg(Thy1-GCaMP6f)7, which expresses the genetic calcium indicator GCaMP6f.
Characterization of the novel model was obtained using Optical Coherence Tomography (OCT) imaging, histology, and ERG recording in the ages of 4, 8 and 12 weeks old. Moreover, optical recordings of RGC function in response to ex-vivo subretinal electrical stimulations were performed.

Results: OCT imaging and histological studies revealed the RD expected in the RCS breed manifested by the decrease in retinal thickness (number of photoreactor rows, average of 10.75±1.24 VS 1.03±0.39 in GCaMP6f-LE and 12 weeks old, $p<0.0001$, respectively) and formation of subretinal debris. ERG recordings demonstrated decrease in the b-wave amplitude with time (518.24±106.83, 291±124.25 and 13.18±4.15μV at 160Cd.s/m2 GCaMP6f-LE, 4 and 8 weeks, respectively) and its absence at 12 weeks old in the GCaMP6f-RCS rat. In addition, subretinal electrical stimulation demonstrated the feasibility of the investigation of activation thresholds and the building of strength-duration curves. Notwithstanding the apparent structural preservation of the retina and in agreement with the ERG recordings, the subretinal activation threshold for the 100usec pulse increased consistently with maturation (15.91±6.64 VS 28±15.13 GCaMP6f-LE and 4 weeks old, $p<0.0001$).

To conclude, this developed breed will prove to be a vital tool in the investigation of the efficacy of vision restoration strategies, such as electrical stimulation with retinal prostheses.

ADAR-based RNA editing and splice-region variants in ABCA4

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Purpose: Use of specially designed guideRNA (gRNA) that harnesses the adenosine to inosine editing potential of the ubiquitous human adenosine deaminase acting on RNA (ADAR) enzyme for site-directed RNA editing (SDRE) is an up-and-coming genetic therapeutic approach for the treatment of inherited retinal diseases (IRDs). Until now, the majority of SDRE research has focused on the recoding of exonic mutations, though many disease-causing IRD variants are in close proximity to or in intronic regions requiring extra tailored design of the gRNAs. As ABCA4 is a gene too large for AAV-based therapy and has many commonly-reported splicing-related variants, we chose ABCA4 variants c.4634G>A, c.5714+5G>A, c.5196+1137G>A/T as targets for SDRE.

Methods: Previously reported midi-gene plasmids harboring either the mutant or WT variant were transfected into ADAR2-overexpressing HeLa cells and subsequently transfected with differing chemically modified gRNAs, considering exonic and pseudoexonic characteristics. Editing and splicing patterns of target RNA were measured through capillary gel-electrophoresis of PCR products and next-generation sequencing (NGS).

Results: Exonic variant ABCA4: c.4634G>A is the last base of exon 31 and was targeted by 60-mer gRNA complementary to either the pre-mRNA or mRNA. There were no negative effects on regular splicing and editing of the target base was measured as 14% and 3% respectively with no additive effects when gRNAs were combined. . Guide RNAs of 59-mer, 39-mer, and 22-mer targeting the exon/intron boundary were designed for analyzing the splice variant ABCA4: c.5714+5G>A within a midigene plasmid and similarly, four different ADAR-recruiting 59-mer gRNAs were designed for editing the deep intronic variants ABCA4: c.5196+1137G>A/T in comparison with a previously reported ASO. These experiments are ongoing, and the results will be presented at the meeting.

Conclusions: In this study we examined the potential of ADAR-based SDRE on ABCA4 splicing-region mutations. We found that RNA editing can be performed on pre-mRNA and mRNA alike, introducing the possibility of editing pre-mRNA to modulate missplicing. We will report on the results of whether the introduction of ADAR2 increases WT splicing efficiency for the c.5714+5G>A and c.5196+1137G>A mutation, as well as editing neighboring nucleotides in proximity to deep intronic mutations such as c.5196+1137G>T to increase WT splicing.

A founder homozygous nonsense mutation in CREB3 causes a variable retinal dystrophy in three North-African Jewish families

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Purpose: Inherited retinal diseases (IRDs) are a large group of heterogenous phenotypes caused by variants in over 350 genes. Despite the integration of next generation sequencing (NGS)-based techniques, diagnosis yield has reached up to 50-70% only. In this study, we aim to confirm the involvement of CREB3 as a novel gene associated with IRDs.

Methods: Whole exome and whole genome sequencing analysis was performed on 8 patients clinically diagnosed with retinitis pigmentosa (RP) or macular degeneration. Homozygosity mapping was performed using the Franklin platform. Skin biopsies were obtained from two homozygous patients and fibroblasts were grown. Expression analysis was done on patient-derived fibroblast cells by reverse transcriptase polymerase chain reaction (RT-PCR) and western blot. Published retinal single-cell RNA data were analyzed. For the localization of CREB3 in the retina, immunohistochemistry staining (IHC) was performed on wildtype mouse retina.

Results: NGS and segregation analysis revealed a homozygous CREB3 nonsense mutation (c.881G>A, p.Trp294*) in 12 patients from three different families. All patients suffered from retinal degeneration with extremely large clinical variability in disease severity and age of onset. The three families are of North African Jewish origin and homozygosity mapping has confirmed that this is a founder mutation among this population. In patients-derived fibroblast cells, the mutant mRNA transcript generated a truncated protein. Expression analysis of CREB3 and IHC have revealed that it is expressed in all cell types of the retina indicating its vital role in photoreceptors function.

Conclusion: We report here for the first time that CREB3 can cause IRDs when mutated. CREB3 is a transcription factor that is predicted to be involved in lipid metabolism, but its retinal function is currently unknown. It was shown previously to be upregulated by UV radiation, which might contribute to the large and unexpected clinical variability observed in this relatively large cohort of patients who are homozygous for the same truncating mutation.

Genetics and IRD

Full updates – 5 minutes

The landscape of mutations causing inherited retinal diseases (IRDs) in the Israeli population

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Purpose: Inherited retinal diseases (IRDs) are a group of over 50 clinically and genetically heterogeneous diseases caused by mutations in more than 300 genes. The Israeli population is very complex and composed of a variety of religious and ethnic groups, leading to great variability in the prevalence of different IRD-causing mutations among these diverse groups. In the current study we analyzed the cause of IRDs in different ethnic groups in the Israeli population to establish the genetic landscape.

Methods: We tabulated the information regarding the cause of disease and ethnic origin of over 2000 solved families included in the Hadassah and Technion. For each ethnic group, we listed the causing mutations and their frequencies and compared it to data available on other populations worldwide.

Results: We identified a total of 1034 disease-causing mutations in Israeli patients with IRDs, including 21 different ethnic groups (14 of which are Jewish), with a total of 4190 familial pathogenic alleles. Founder mutations contributed the largest proportion of alleles in Yemenite Jews, followed by North African and Ashkenazi Jewish populations. The most common mutation was FAM161A-c.1355_6delCA, a founder mutation in multiple Jewish ethnic groups. While some founder mutations show population specificity (i.e. MAK-c.1297_8ins353 and DHDDS-c.124A>G in Ashkenazi Jews, CERKL- c.238+1G>A, in Yemenite Jews, and TRPM1- c.880A>T in Arab-Muslims), other were pan-ethnic and are likely to represent ancient alleles (i.e. ABCA4- c.5882G>A and NR2E3- c.932G>A). Comparison of the mutation spectrum of IRD mutations identified in Ashkenazi Jews to gnomAD data revealed similarity mainly to the mutation spectrum identified in Europeans.

Conclusions: Our analysis provides a comprehensive list of common and founder mutations for each ethnic group in Israel and is likely to allow more accurate and informative genetic counseling for Israeli families with IRDs. Our future plan is to provide the genetic counseling community a searchable database depicting the most common mutations for each IRD phenotype in each studied ethnic group.

Mutations in PRPF31 are associated with mitochondrial dysfunction in human RPE

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Purpose: Heterozygous mutations in the gene encoding the RNA splicing factor pre-mRNA processing factor 31 (PRPF31) are a leading cause of incurable blinding retinitis pigmentosa (RP). In vitro, whole transcriptome analysis revealed that PRPF31 mutations are associated with the mis-splicing of thousands of genes, including mitochondrial genes. However, whether these splicing defects are associated with defects in mitochondrial function in the human retina remains unknown. This study aims to investigate the association between PRPF31 mutations and mitochondrial function in human induced pluripotent stem cells (iPSC)-derived retinal pigment epithelium (RPE) models.

Methods: Mitochondrial function was assessed in fully differentiated PRPF31-RP iPSC- RPE models using the Agilent Seahorse XFe96-Pro Analyzer. This state-of-the-art system measures the oxygen consumption rate (OCR) and extracellular acidification rate (ECAR) of live cells. The OCR provides information about mitochondrial health and energy production. Together, these measurements provide a systems-level view of cellular metabolic function in cultured cells.

Results: A protocol for testing mitochondrial function in fully differentiated RPE models was established. The basal and maximal OCR were lower in the RPE models of two PRPF31-RP patients compared to the healthy control. However, treating the PRPF31 RP patient-derived RPE cells with a drug identified by a high-throughput drug screen that elevates the expression of the PRPF31 WT allele increased basal and maximal OCR by two-fold.

Conclusions: This study suggests a link between PRPF31-RP and mitochondrial dysfunction and may lead to the identification of tailored therapeutic interventions. It may advance personalized therapies for PRPF31 and various forms of RP, thereby contributing to precision medicine.

Using minigene-based splice assays to evaluate the pathogenicity of variants identified in patients with inherited retinal diseases

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Purpose: Inherited retinal diseases (IRDs) are a clinically and genetically heterogeneous group of blinding diseases, with approximately 1:1300 affected individuals worldwide. Currently, the most effective approach to genetically diagnose IRD patients is next-generation sequencing (NGS). However, in some patients, rare variants in relevant IRD causal genes are identified, but with uncertain significance (VUS). Some of those VUS may lead to abnormal RNA splicing and improper protein production.

Methods: The pathogenicity of VUS was tested using a minigene-based in vitro assay. In this assay, the relevant gene segments (exons and introns) are inserted into an expression vector and transfected into human cultured cells (HeLa). 24 hr following transfection, the RNA is extracted from the cells and reverse transcribed (RT). Then, the cDNA is subjected to PCR amplification. PCR products are subjected to agarose gel electrophoresis and sequenced.

Results: Five variants in IRD related genes were evaluated. In three cases, we found a difference between WT and mutant splicing products, while in two other cases there was no significant difference. The changes that were observed in splicing were intron retention, exon skipping and the use of new or cryptic slicing sites. These changes often led to generation of premature stop codons.

Conclusions: We identified three VUS that cause changes in splicing. Those splicing changes, even if partial, are predicted to disrupt protein activity. These findings demonstrate how VUS can lead to protein abnormalities, which would lead to pathological outcomes. Moreover, understanding the effect of VUS will contribute to better diagnostics and genetic counseling.

Clinical characterization of RP11 patients and asymptomatic carriers in Israel

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Purpose: RP11 is caused by mutations in the PRPF31 gene, encoding a pre-mRNA splicing factor. Disease severity may vary even between carriers of the same mutation. Deciphering the association between the PRPF31 mutation and the natural history of the disease is essential for designing future clinical trials. Here, we analyzed inter-familial and intra-familial variations in the natural history of the disease in Israeli RP11 patients carrying heterozygous nonsense mutations, frameshifts, a splice site mutation, large deletions, and an exon insertion.

Methods: Twenty-six patients (age 2-84 years) from 17 Israeli PRPF31-RP families underwent a complete ophthalmic assessment, including best-corrected visual acuity (BCVA), spectral domain-optical coherence tomography (SD-OCT) imaging, and electroretinography (ERG). Nine patients returned for one to eleven follow-up visits within one to ten years.

Results: Seventeen patients had the nonsense mutation c.1108G>T;p.E370*, one had a frameshift mutation (c.689delA, ;p.K230Rfs*9), four had a large deletion in exon 1, two had a splice site mutation (c.697+1G>A), and one had a non-frameshift insertion of 24 nucleotides. (c.A820insTCGTGACATCTACCACATCGTACG). One patient carried the nonsense c.1165C>T;p.Q389* mutation and additional probably harmful heterozygous mutations in the MERTK (c.773C>A;p.A258E) and RIMS1 (c.1088G>T;p.R363L) genes. This patient presented with a relatively mild phenotype with slow progression. SD-OCT ellipsoid zone length deteriorated at a mean rate of -0.044mm/year (95% CI: 0.07-0.019), and the ellipsoid zone area deteriorated at a mean rate of -5.1%/year (95% CI 2.76-7.3). ERG b-wave deteriorated faster than the a-wave (mean -7.6% vs. -3.5 % /year). Three subjects with a c.1108G>T mutation and one with a deletion in exon one were asymptomatic with normal BCVA but reduced ERG amplitudes and structural abnormalities on OCT.

Conclusions: In this Israeli RP11 cohort, disease severity and deterioration rate varied between patients, even among individuals with the same mutation. Nonsense mutations showed similar severity and deterioration rate as insertions/ deletions/ frameshifts, and asymptomatic carriers showed subclinical disease manifestations."

C19ORF44 is a novel gene which encodes a nuclear protein and is associated with autosomal recessive retinal dystrophy

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Purpose: The current work aimed to identify the genetic cause for inherited retinal dystrophy (IRD) in a subset of Israeli patients, to characterize their retinal phenotype, and the properties of the underlying gene and protein.

Methods: Study participants underwent a comprehensive ophthalmological evaluation, including best-corrected visual acuity, visual field testing, fundus autofluorescence, optical coherence tomography and electroretinography. Genetic analysis included exome sequencing and Sanger sequencing. Reverse transcription-PCR was used to analyze gene expression pattern in human and mouse tissues. Intracellular localization of the encoded protein was examined by immunostaining of cultured cells (HeLa and hTERT RPE-1).

Results: One homozygous rare frameshift variant (c.549_550del) in the C19ORF44 gene was identified in nine IRD patients from seven unrelated families, five of which were of Yemenite Jewish descent and two of Ashkenazi Jewish origin. All homozygous individuals were affected with autosomal recessive rod-cone dystrophy, characterized by a patchy perifoveal chorioretinal atrophy. Study participants had constricted visual fields, and macular OCTs showed significant perifoveal outer retinal loss. Nonetheless, most patients had good visual acuity, despite their being on their 7th decade, indicating that the retinal disease probably has a slow progressive course. The C19ORF44 gene is expressed in various human tissues, including the retina. In the mouse eye its expression is upregulated post-nataly. Immunostaining revealed that C19ORF44 is a nuclear protein, but is missing from mitotic nuclei.

Conclusions: Although the function of C19ORF44 in the retina remains to be studied, our findings suggest that it might be involved in cell cycle regulation. Based on our results, C19ORF44 is crucial for normal human retinal function and is a novel IRD-causative gene, associated with a unique clinical phenotype of patchy perifoveal chorioretinal atrophy.

ADAR enzyme – mediated RNA editing as a therapeutic tool for choroideremia

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Purpose: Mutations in CHM, encoding Rab escort protein-1 (REP1), are known to cause choroideremia. In this study, we aimed to investigate the efficacy of guide RNAs (gRNAs) targeting two common CHM nonsense mutations: c.877C>T, identified in our cohort, and c.1218C>A, that is relatively common worldwide, by recruiting the endogenous adenosine deaminase acting on RNA (ADAR) enzymes to edit mutant RNA transcripts.

Methods: Both CHM nonsense mutations are challenging for RNA editing due to the presence of a Guanine upstream of the target Adenine. Therefore, two gRNAs were designed for each mutation. The first gRNA contains a single mismatch across the target A and the second gRNA contains a double mismatch across the target A and upstream G. For each mutant CHM sequence, a minigene plasmid construct was generated. In addition, another plasmid with the target mutant CHM sequence upstream to a stem-loop structure including the gRNA in cis was constructed. HeLa cells overexpressing ADAR were transfected with either the minigene-carrying plasmid and the single/double mismatch gRNA specifically designed to its target transcript, or with the stem-loop plasmid endogenously generating the required gRNA. RNA editing levels were estimated by RT-PCR followed by next generation sequencing (NGS).

Results: The presence of a double mismatch in the gRNA was more efficient for RNA editing compared to a single mismatch. In cells transfected with the CHM c.877C>T construct, 5% of mutant bases were corrected using the endogenous gRNA with a single mismatch. double mismatch gRNA improved editing levels to 15%. Cloning the same mutation into the stem-loop structure resulted in higher RNA editing levels of 14% for a single mismatch gRNA and 63% for the double mismatch. In cells transfected with the CHM c.1218C>A minigene and the appropriate endogenous gRNAs, RNA editing levels were evaluated at 1% (single mismatch) and 2% (double mismatch). Stem-loop structures results in higher editing levels of 16% (single mismatch) and 55% (double mismatch).

Conclusions: We provide here evidence for the feasibility of RNA editing to edit or correct choroideremia-causing mutations. Additional experiments are needed to identify the most efficient gRNAs. This could be performed using our competitive gRNA selection tool in yeast to design millions of possible gRNAs for each of the two mutations as well as a library of hundreds of gRNAs to identify the most efficient gRNAs in HeLa cells.

Disruption of common ocular developmental pathways in patient-derived optic vesicle models of microphthalmia

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Purpose: Eye morphogenesis is tightly regulated by a highly conserved genetic network that when disrupted, can result in severe ocular malformation on a spectrum known as microphthalmia, anophthalmia and coloboma (MAC). While over 100 genes are associated with MAC, little is known about shared disease mechanisms. This study aimed to identify aberrations to ocular development pathways common to microphthalmia patients with distinct pathogenic variants. Due to the high rate of unsolved cases, the elucidation of these shared disease pathways may reveal novel candidate genes for future genetic diagnoses.

Methods: Patient-specific (PAX6-associated microphthalmia p.(Asn124Lys) and an unsolved microphthalmia patient) and healthy control iPSC-derived optic vesicles (OVs) were generated using two clones from each line to model ocular development until day 50. Gene and protein expression were assessed through RNA-seq, RT-qPCR, immunohistochemistry, western blot and ELISA. Apoptosis was detected using the terminal deoxynucleotidyl transferase dUTP Nick-End Labeling (TUNEL) assay and proliferating cells detected by mitosis marker pH3 staining. Apoptosis, cell proliferation and vesicle diameter were quantified using ImageJ.

Results: At all time points, microphthalmia OV diameters were significantly smaller than healthy controls. TUNEL staining revealed a significant increase in apoptotic cells in patient OVs while pH3 staining revealed decreased cell proliferation. RNA-seq analysis highlighted global upregulation of pro-apoptotic genes in microphthalmia OVs. Downregulation of Notch ligands DLL1 and DLL3 and effectors HES1 and HES5 suggest aberrant Notch signalling in microphthalmia and resulted in differential expression of Notch target genes such as MITF and HDAC1. Additionally, the increased production of extracellular matrix (ECM) proteins was detected in microphthalmia OVs.

Conclusions: The ‘small eye’ microphthalmia phenotype can be recapitulated in vitro in patient-derived optic vesicles. Reduced cell proliferation and increased apoptosis in microphthalmia patient-derived optic vesicles were observed, possibly contributing to the small eye phenotype. Disruptions to Notch signalling may contribute to a global increase of ECM production and further dysregulation of key early ocular developmental genes. Additionally, abnormally high production of ECM in microphthalmia patients may overly restrict optic vesicle growth, resulting in ocular malformations.

Diverse Ancestry Analysis: The IAMDGC 2.0

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Purpose: The previous genome-wide association (GWAS) analysis from the International Age-related Macular Degeneration Genomics Consortium (IAMDGC) based on 1000G-imputed data focused on 33,976 unrelated European (EUR) individuals and identified 52 independent variants from 34 loci for late AMD. Higher genetic coverage from TOPMed-imputed data and inclusion of individuals from other ancestries provide opportunities for an update of this analysis.

Methods: We here present a revisited analysis of IAMDGC data (IAMDGC 2.0) imputed to TOPMed-reference data (v2 imputation panel, build 38). Ancestry of each individual was determined by clustering its first two principal components with those from reference individuals from the Human Genome Diversity Project to define Asian (ASN), African (AFR), European (EUR), and unspecified other ancestry (OTH). By this, we identified 15,616/16,723 EUR, 207/322 ASN, 50/357 AFR, and 235/636 OTH cases of late AMD and AMD-free controls, respectively. We conducted ancestry-specific GWAS analyses of related and unrelated individuals adjusted for the first two PCs using a Firth test implemented in regenie and meta-analyzed the GWAS results with METAL. The total number of genetic variants analyzed (MAF>0.1, INFO>0.8) was 51,162,741 across ancestries.

Results: Among the 34 lead variants, we found a significant association for the HTRA1/ARMS2 locus (P<0.05/34=0.0015) for AFR, ASN, and EUR (OR=2.03, 95%CI=1.34-3.08; OR=2.23, 95%CI=1.68-2.95; OR=2.93, 95%CI=2.82-3.04 respectively). We did not find a significant association for CFH in the AFR population OR=0.81, 95%CI=0.53-1.26) but did in the ASN population(OR=0.57, 95%CI=0.42-0.76), and in the EUR(OR=0.38, 95%CI=0.36-0.39). Among the 34 lead SNPs, allele frequencies varied significantly in AFR or ASN compared to EUR (P<0.05/34=0.0015; 20/34 loci in ASN, 25/34 loci in AFR, Z-score 2 population testing). The cross ancestry meta-analysis did not yield any further genomic significant loci besides for the original 34 loci. In the meta-analysis, CFH and HTRA1/ARMS2 were in the same direction across ancestries, with a heterogeneity P-value of 0.001 and 0.01 respectively.

Conclusions: It is important to extend GWAS for advanced AMD to diverse ancestries. Our results support the ARMS1/HTRA2 locus as the strongest genetic locus for AMD in diverse ancestries with comparable ORs. Our results also document differential frequencies amongst different ancestries with AMD.

A novel large deletion in chromosome X is associated with nystagmus in male and female members of an extended family

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Purpose:
Large kindred of Bedouin ancestry presented with apparently autosomal-dominant infantile nystagmus affecting individuals of both genders. We investigated the clinical presentation and molecular basis of infantile nystagmus in the kindred.

Methods:
Affected individuals underwent a thorough ophthalmic examination. Whole exome sequencing (WES) data of an affected individual were filtered using Franklin by Genoox Platform (https://franklin.genoox.com). We then employed BAMdelbee, a tool generated in our lab for detecting homozygous deletions in WES and whole genome sequencing (WGS) data by pinpointing regions covered in control samples but not in the tested samples.

Results:
Eight clinically affected individuals were identified in this family, 6 of whom were female. Patient ages ranged between 5 and 68 years. The clinical presentation was similar among both genders. All had nystagmus which in some of them was accompanied by anomalous head posture or nystagmus blockage by convergence. Visual acuity ranged between 6/9 and 6/60. Refractive errors varied among patients, and most had mild to moderate hyperopia and astigmatism. No systemic abnormalities were detected except a congenital heart defect in one patient and Crohn's disease in another. Thyroid function tests were normal in all patients.
Using BAMdelbee, we identified a 1.4Mbp deletion on chromosome X (ChrX:130755821-132199819) in an affected individual. This deletion encompassed FRMD7 and 5 other genes in its vicinity (ENOX2, ARHGAP36, IGSF1, OR13H1, STK26), including IGSF1 that has been previously associated with X-linked recessive central hypothyroidism.

Conclusion:
In a kindred presenting with apparently autosomal dominant nystagmus affecting both males and females, we identified a large pathogenic deletion on chromosome X, including the FRMD7 gene. Notably, although the deletion encompassed neighboring genes, the patients exhibited isolated nystagmus. Clinicians and genetic counselors should be aware that female patients may exhibit clinically evident X-linked nystagmus, and that chromosomal microarrays (CMA) should be considered as part of the genetic workup in nystagmus.

Autistic spectrum disorder and psychomotor delay in retinoblastoma patients

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Retinoblastoma (Rb) mostly results from a mutation in the Rb1 gene on the long arm of chromosome 13 (Ch. 13q14). About 5-10% of cases are due to gross-sized molecular deletions in Ch.13q termed 13q deletion syndrome. The deletions can involve the surrounding genes delineating a contiguous gene syndrome characterized by RB, developmental anomalies, and peculiar facial dysmorphisms. There have also been reports of certain MRI structural brain abnormalities found in these patients. Other than a single brief case report of a patient with a 13q deletion sporadic Rb and autism spectrum disorder (ASD), we found no other reports linking these conditions, except for a molecular link of an interaction between the retinoblastoma protein and the lysine demethylase 5A (KDM5A) gene, also called the ASD gene which lies in chromosome 12. Here, we describe a series of retinoblastoma patients with ASD or psychomotor delay.

Methods: A retrospective review of the medical records of children treated for retinoblastoma at the Hadassah Ocular Oncology Unit.

Results: From 1994 to 2021, we treated 300 children with retinoblastoma. Ten boys were diagnosed with psychomotor disabilities: two are high-functioning autistics whose germline Rb1 status was not found, one has a 13q deletion with ASD (and his mother with the same deletion, but almost completely neurotypical), one autistic with a two-point mutation, two with a 13q and mental retardation, three with 13q deletion and severe psychomotor delay. In addition, we diagnosed one girl with a 13q deletion and retinocytoma in one eye that remained unchanged in 8 years of follow-up. Overall, we found six children with ASD and five with psychomotor delay.

Conclusions: Visual disturbances may hinder the diagnosis of ASD as a reason for failing to form eye contact. However, retinoblastoma may present with ASD and with more severe psychomotor delays, mostly in patients with a 13q deletion. A multi-disciplinary retinoblastoma team should be aware of this possibility and be ready with diagnostic and support plans for these conditions.

The Influence of Age and Sex on Cataract Surgery Complications and Outcomes

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Purpose - Cataract surgery, a very common and critical procedure for restoring vision, has outcomes that can vary based on patient demographics. This study aimed to elucidate the effects of age and sex on the risk factors, intraoperative complications, and postoperative outcomes of cataract surgery.

Methods - Conducted as a single-center retrospective cohort study, it analyzed 691 eyes from 589 individuals who underwent surgery at a tertiary referral center, utilizing data from electronic medical records to assess preoperative risk factors, intraoperative complications, and pre- and post-operative best-corrected visual acuity (BCVA) along with demographic data.

Results - The main results highlighted that males aged 65-75 years exhibited significantly higher rates of functional postoperative BCVA (91% for males vs. 79% for females, p=0.007). Differences in surgical complications or risk factor prevalence do not explain this disparity. Furthermore, the study identified age-specific thresholds where BCVA improvements significantly declined, beyond 65 years for females and 75 years for males. The likelihood of worsened BCVA post-surgery increased with age for both sexes, with a significant decline in BCVA improvement transitioning from 55-65 years to 65-75 years age groups.

Conclusions - The findings underscore the critical influence of both sex and age on cataract surgery outcomes, revealing significant sex-specific age thresholds that signal lesser improvements in postoperative BCVA. These insights advocate for integrating patient age and sex into preoperative evaluations to better tailor the timing and planning of cataract surgery, ultimately aiming to optimize clinical outcomes.

Results of Cataract Surgery in Eyes with Adult-Onset Foveomacular-Vitelliform Dystrophy (AFVD)

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Purpose: To report the outcomes and safety of cataract surgery in AFVD eyes.

Methods: Data was collected retrospectively on AFVD eyes that underwent cataract surgery. Eyes with dry and neovascular AMD (NVAMD) that had cataract surgery served as controls. The primary outcome was visual acuity improvement. A secondary outcome was the development of choroidal neovascularization (CNV) or retinal atrophy. Data collection included demographics, best-corrected visual acuity LogMAR (VA), results of eye exams, and optical coherence tomography.

Results: The study included 79 eyes (27 dry AMD, 38 NVAMD, 14 AFVD).
VA of AFVD before surgery (0.62±0.36) was statistically different 1 month (0.23±0.12) or over 12 months post-surgery (0.26±0.12); p=0.014 and P=0.012 respectively. 12 months post-surgery, no CNV occurred. No major changes in AVFD stage were noted.
No difference was found comparing VA improvement one month after surgery of dry AMD, NVAMD and AFVD (dry AMD=0.47±0.68; NVAMD=0.28±0.37, AFVD=0.39±0.38, P=0.30). in the dry AMD group, one eye developed CNV 10 months after surgery and one eye had worsening retinal atrophy one month post-surgery.

Conclusion: Following cataract surgery, mean VA improved significantly in eyes with AFVD (0.39) and no CNV or new-onset retinal atrophy developed. There were no differences in VA improvement over one month between AFVD, dry AMD and NVAMD groups. These findings indicate the safety and efficacy of cataract-surgery in AFVD eyes.

Benchmark of cataract segmentation architecture for Artificial Intelligence

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Background:
Cataract is a leading cause of vision impairment and blindness worldwide. Accurate grading of cataract is essential. Lens Opacities Classification System III (LOCS III) is used clinically for grading lens opacification. This results in subjective assessments that differ among ophthalmologists. With the advancement of imaging, intraocular lens calculation formulas, vast amounts of data, and the implementation of AI in ophthalmology, cataract grading can become more objective and standardized. In supervised AI models, segmentation of anatomic structures of the lens based on OCT images is the first step for training AI models for objective cataract assessment.

Aim:
This study aims to evaluate SOTA (state-of-the-art) segmentation models in relation to different amounts of images in the training set for cataract lens segmentation.

Methods:
Preoperative SS-OCT (Swept-Source Optical Coherence Tomography) anterior segment images were analyzed and preprocessed to identify the anatomic structures of the crystalline lens according to the 3 subgroups of cataract: cortical, nuclear, and posterior subcapsular.
The data was allocated by a ratio of 8:1:1 for training, validation, and testing.
Three SOTA models (U-met, Yolov8, and Segformer) were used to segment the SS-OCT image of a cataract lens. Each model was trained six times with an increasing amount of images in the training set (60,125,250,500,1000,2150).
The models' performance were analyzed using intersection over union (IOU), DICE similarity coefficient, precision, and recall parameters.

Results:
Overall, 18 models were constructed using 2150 SS-OCT images of different eyes.
The nuclear and cortical segmentation achieved higher IOU and DICE performance using the U-net compared to others, regardless of the amount of images in the training set ($p<0.001$). The posterior subcapsular segmentation achieved a higher IOU and DICE performance using the Yolo architecture for the groups of training sets ($P<0.001$). Increasing the amount of images in the training statistically improved the IOU and DICE by 95% (171 out of 180) of comparisons performed.

Conclusion:
Objective cataract assessment using AI-based cataract segmentation was achieved using a smaller dataset. This insight can guide future studies in constricting expert segmented data when aiming at standardized cataract grading.

4485-3p MicroRNA as biomarker for uveitis in juvenile idiopathic arthritis

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Purpose: We aim to explore micro-ribonucleic acids (miRNAs) expression in JIA-U and to examine their possible role as predictive biomarkers.

Methods: miRNA expression profiling was performed on peripheral blood mononuclear cells of pediatric patients with either JIA, JIA-U, and uveitis. The first cohort of patients' samples were analyzed using the multiplexed NanoString miRNA expression assay, while the final cohort was analyzed by high-throughput small-RNASeq. Patient- and disease-related data was retrieved retrospectively from patients' medical files.

Results: There were 35 children participated in the study, among them 20 with JIA-U, with either active (n=8) or inactive (n=12) disease, 10 patients with JIA without ocular involvement and a control group of patients with other types of uveitis (n=5) including active (n=4) and inactive (n=1) disease. Mean age was 8.6 years (range 1.9-17.9 years) with most being females (29, 83%). Immunomodulatory treatment was given to 19 patients (54%). Significant differential expression was found for miR-4485-3p. In patients with JIA-U and those with only uveitis, miR-4485-3p was significantly increased compared to patients with JIA ($p<0.05$). No difference in miR-4485-3p levels was observed between patients with either active or inactive uveitis.

Conclusions: This study is the first to demonstrate different expression profiles of a specific miRNA in JIA patients with and without uveitis. If verified in larger studies, these findings may enable to identify JIA patients prone to develop uveitis and detect disease activity.