RETeval®
ERG SIMPLIFIED

RET*eval* Clinical Abstract List

Peer-reviewed publications with and about the RET*eval*® device addressing diseases of the human eye

Disclaimer
All publications that investigate or use the RET*eval* device are listed in this document and grouped per indication. For each publication the abstract is provided.

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Content

Quality Review and General information

Kato K. et al. Effect of Pupil Size on Flicker ERGs Recorded with RETeval System: New Mydriasis-Free Full-Field ERG System, 2015

PURPOSE: We studied whether pupil size affects the flicker electroretinograms (ERGs) recorded by RETeval, a new mydriasis-free full-field flicker ERG system.

METHOD: We studied 10 healthy subjects. The RETeval manufacturer claims that the system delivers a constant flash retinal illuminance by adjusting the flash luminance to compensate for changes in the pupil size. Two experiments were performed. First, the flicker ERG was recorded every 3 minutes after the instillation of mydriatics. Second, the flicker ERG was recorded while the subjects wore soft contact lenses with two different artificial pupil sizes.

RESULTS/CONCLUSION: The first experiment showed that as pupil size increased, the amplitudes of the fundamental component of the flicker ERG did not change significantly, but the implicit times of the fundamental component were significantly prolonged for larger pupil sizes. There was a significant positive correlation between the pupillary area and implicit time of the fundamental component ($r=0.93$, $P < 0.001$). The second experiment showed that the implicit times of the fundamental component in the flicker ERG were significantly longer with larger artificial pupil.

The results suggest that the effective retinal illuminance of the stimulus delivered by the RETeval system decreases for large pupil sizes. However, in most clinical testing situations, patients' undilated pupils will likely be sufficiently small to fall within the range for which the system delivers a stimulus of constant retinal illuminance.

Asakawa K. et al: New Mydriasis-Free Electroretinogram Recorded with Skin Electrodes in Healthy Subjects, 2017

PURPOSE: To evaluate the reproducibility and consistency of the new mydriasis-free electroretinogram (ERG) with a skin electrode (RETeval) device, to determine the normative values of parameters, and to clarify the usefulness of pupil records to colored-light stimulus

METHOD: A total of 100 eyes of 50 healthy subjects (mean age, 21.4 years) were enrolled. The diagnostic parameters obtained by the RETeval device were examined under the following conditions. The reproducibility was determined with the coefficient of variation (CV). The consistency was examined by intraclass correlation coefficients (ICCs). The mean value and the normal range were analyzed with a 95% confidence interval as the normative values of parameters. The correlation of parameters to pupil records (area ratio, constriction ratio) and flicker ERG was also examined in the diabetic retinopathy assessment protocol.

RESULTS/CONCLUSION: From the CV for each of the two measurements, the amplitude has a low reproducibility compared with the implicit time. Generally good consistency was obtained with both ERG parameters (ICCs = 0.48–0.92). Moderate correlations were found for the white-, red-, and blue-light stimulus in the area ratio and the constriction ratio, respectively (r = 0.44–0.62; P = 0.010–<0.0001). No correlation was observed between pupil and flicker parameters (r = 0.06–0.34; P = 0.646–0.051). The RETeval device was suggested as a possible screening device to detect the visual afferent diseases by evaluating in combination with the ERG recording and the colored-light pupil response.

Davis Q.C. et al. Constant luminance (cd·s/m2) versus constant retinal illuminance (Td·s) stimulation in flicker ERGs, 2017

PURPOSE: To compare the effect of variable pupil size on the flicker electroretinogram (ERG) between a stimulus having constant luminance and a stimulus having constant retinal illuminance (constant Troland) that compensates for pupil size.

METHOD: Subjects (n = 18) were tested with 12 pairs of the stimuli. The stimulus pair consisted of the ISCEV standard constant luminance stimulus (3 cd·s/m2 with a 30 cd/m2 background) and a constant retinal illuminance stimulus (32 Td·s with a 320 Td background) selected to provide the same stimulus and

background when the pupil diameter is 3.7 mm. Half the subjects were artificially dilated, and their response was measured before and during the dilation. The natural pupil group was used to assess intra- and inter-subject variability. The artificially dilated group was used to measure the flicker ERG's dependence on pupil size.

RESULTS/CONCLUSION: With natural pupils, intra-subject variability was lower with the constant Troland stimulus, while inter-subject variability was similar between stimuli. During pupil dilation, the constant Troland stimulus did not have a dependence on pupil size up to 6.3 mm and had slightly larger amplitudes with longer implicit times for fully dilated pupils. For the constant luminance stimulus, waveform amplitudes varied by 22% per mm change in pupil diameter, or by 48% over the 2.2 mm diameter range measured in dilated pupil size. There was no difference in inter-subject variability between constant Troland natural pupils and the same subjects with a constant luminance stimulus when dilated (i.e., the ISCEV standard condition).

These results suggest that a constant Troland flicker ERG test with natural pupils may be advantageous in clinical testing. Because of its insensitivity to pupil size, constant Troland stimuli should produce smaller reference ranges, which in turn should improve the sensitivity for detection of abnormalities and for monitoring changes. In addition, the test can be administered more efficiently as it does not require artificial dilation.

Kato K. et al. Factors Affecting Mydriasis-Free Flicker ERGs Recorded with Real-Time Correction for Retinal Illuminance: Study of 150 Young Healthy Subjects, 2017

PURPOSE: The purpose of this study was to determine what factors affect the fundamental components of the flicker ERGs recorded by RETeval in young healthy subjects.

METHOD: Flicker ERGs were recorded with the RETeval system from 150 eyes of 150 young healthy subjects (age, 20–29 years). Univariate and multivariate linear regression analyses were performed to identify the factors that affected the implicit times and amplitudes of the fundamental component of the flicker ERGs. The independent variables included age, sex, refractive error, axial length, and pupillary area.

RESULTS/CONCLUSION: Multivariate regression analyses indicated that a longer axial length (P = 0.03) and larger pupillary area (P = 0.008) were independent factors that were significantly associated with longer implicit times of the fundamental component of the flicker ERGs. Multivariate regression analyses also showed that the female sex (P = 0.03) was an independent factor, which was significantly associated with larger amplitude fundamental component of the flicker ERGs. These results indicate that the fundamental components of the RETeval flicker ERGs are significantly affected by the axial length, pupillary area, and sex of young healthy subjects.

Hobby A.E. et al. Effect of varying skin surface electrode position on electroretinogram responses recorded using a handheld stimulating and recording system, 2018

PURPOSE: A handheld device (the RETeval system, LKC Technologies) aims to increase the ease of

electroretinogram (ERG) recording by using specially designed skin electrodes, rather than corneal electrodes. We explored effects of electrode position on response parameters recorded using this device.

METHOD: Healthy adult twins were recruited from the Twins UK cohort and underwent recording of light adapted flicker ERGs (corresponding to international standard stimuli).

In Group 1, skin electrodes were placed in a "comfortable" position, which was up to 20 mm below the lid margin. For subsequent participants (Group 2), the electrode was positioned 2 mm from the lid margin as recommended by the manufacturer.

Amplitudes and peak times (averaged from both eyes) were compared between groups after age matching and inclusion of only one twin per pair. Light-adapted flicker and flash ERGs were recorded for an additional 10 healthy subjects in two consecutive recording sessions: in the test eye, electrode position was varied from 2 to 10–20 mm below the lid margin between sessions; in the fellow (control) eye, the electrode was 2 mm below the lid margin throughout. Amplitudes and peak times (test eye normalised to control eye) were compared for the two sessions.

RESULTS/CONCLUSION: Flicker ERG amplitudes were significantly lower for Group 1 than Group 2 participants ($p = 0.0024$). However, mean peak times did not differ between groups ($p = 0.54$).

For the subjects in whom electrode position was changed between recording sessions, flash and flicker amplitudes were significantly lower when positioned further from the lid margin ($p<0.005$), but peak times were similar ($p>0.5$).

Moving the skin electrodes further from the lid margin significantly reduces response amplitudes, highlighting the importance of consistent electrode positioning. However, this does not significantly affect

peak times. Thus, it may be feasible to adopt a more comfortable position in participants who cannot tolerate the recommended position if analysis is restricted to peak time parameters.

Miura G. et al. Flicker electroretinograms of eyes with cataract recorded with RETeval system before and after mydriasis, 2018

PURPOSE: The aim of this study is to determine the effect of pupil size of eyes with cataracts on the flicker electroretinograms (ERGs) elicited and recorded with the RETeval system.

METHOD: Forty-one eyes of 41 patients (mean age, 76.5±7.3 years) that had grade 2 nuclear or cortical cataract without any other abnormalities were studied. Flicker ERGs were recorded before and after mydriatic drops instillation. The ERGs were elicited by the white light delivered at the frequency of 28.3 Hz and intensities of 2, 8, and 32 Td-s. The amplitudes and the implicit times of the flicker ERGs before and after mydriasis were compared.

RESULTS/CONCLUSION: There were no significant differences between the amplitudes before and after mydriasis (P=0.35, 2 Td-s; P=0.31, 8 Td-s; P=0.50, 32 Td-s). There were also no significant differences between the implicit times before and after mydriasis (P=0.86, 2 Td-s; P=0.98, 8 Td-s; P=0.95, 32 Td-s). The mean amplitudes and implicit times of the nuclear and cortical cataracts groups before the mydriasis were also not significantly different from those after mydriasis for all stimulus intensities.

The lack of significant differences in the amplitudes and the implicit times of the flicker ERG of cataractous eyes before and after mydriasis indicated that the RETeval flicker ERGs in cataractous eyes is less affected by the pupil diameter. With our earlier study, it was assumed that the effect of cataracts on the RETeval flicker ERGs was due to the opacity of the crystalline lens, and the influence of the cataract would not be reduced or increased by mydriasis.

Samoto, D et al. The Effect of Age on Full-Field Electroretinograms Recorded with Skin Electrodes, 2020

OBJECTIVES: The aim of this study was to determine whether age correlates with amplitude and latency, when full-field electroretinography (ERG) is performed using skin electrodes. The ability of pulse reference power line noise reduction (PURE) to dampen the noise associated with the use of skin electrodes, was also investigated.

METHODS: ERG was performed on 77 eyes in 77 healthy subjects (mean age: 55.6±19.0 years; age range: 9 to 86 years). Subjects with −5D or higher myopia, Emery-Little grade III or higher cataracts, retinal disease, uveitis, glaucoma, ≤5 mm mydriasis, or a history of intraocular surgery other than cataract surgery, were excluded. The active, reference, and ground electrodes were placed on the lower eyelid, outer canthus, and earlobe, respectively. Responses were averaged 10 times for dark-adapted (DA) ERGs, and 32 to 64 times for light-adapted (LA) ERGs. Noise was removed using the PURE method.

RESULTS: The DA ERGs without PURE were so noisy that the amplitude or latency could not be determined, whereas those with PURE were comparatively quieter. ERG with PURE demonstrated a significant negative correlation between age and amplitude and a significant positive correlation between age and latency.

CONCLUSIONS: We could record the measurable ERG waveforms with skin electrodes by using the PURE method, especially in fewer averaged conditions. It is suggested that skin electrode with PURE is suitable to examine the pathological ERGs, and other types of electrodes. It is recommended that the aging effect should be taken into consideration when pathological ERGs are evaluated.

Carter, P. et al. Comparison of the Handheld RETeval ERG System with a Routine ERG System in Healthy Adults and in Paediatric Patients, 2020

PURPOSE: Electroretinograms (ERG) are necessary for the evaluation of retinal function, however testing children is challenging and only performed at a few specialised centres. The handheld RETeval ERG instrument could prove a valuable tool for clinicians in assessing retinal function. This study evaluates this device using an ISCEV approved modified paediatric protocol and compares it to standard methods using a photic stimulator.

METHOD: Cone and rod ERGs were recorded using a standard photic stimulator (Grass) and the RETeval device. Both methods involve using skin electrodes, without**K** mydriasis and under dark and light conditions.

Two groups of participants were recruited: 44 healthy adult subjects (mean age = 39 years) and 37 paediatric patients (mean = 5 years). Three of the paediatric patients were not sufficiently compliant to undertake the RETeval recording.

RESULTS: Adult ERG reference range data are presented for the RETeval and compared to the standard system. There is lack of absolute agreement in the measurements between the two devices, highlighting the need for device-specific reference data. In the paediatric group there is a high level of diagnostic agreement between both systems (Cohen's Kappa k = 0.80). The relative sensitivity and specificity of the RETeval was 1.0 and 0.91. Qualitative patient and user feedback is discussed.

CONCLUSIONS: ERGs are similar between the two methodologies. This study demonstrates that the RETeval device is a useful tool for assessing retinal function in children. Importantly, it is quick, relatively easy to use and can potentially reduce the burden and costs of paediatric electrodiagnostic assessments.

Sugawara. et al. Effects of Recording Sequence on Flicker Electroretinographics Recorded with Natural Pupils Corrected for Pupil Area, 2020

PURPOSE: The purpose of this study was to determine whether the sequence of the ERG recordings will alter the results.

METHODS: We studied 30 eyes of 30 healthy subjects. The flicker ERGs were recorded with the RETeval system without mydriasis and were elicited by 8, 16 and 32 photopic Td-s. The flicker ERGs were recorded at two sessions. Session 1, the ERGs were recorded from the right eye and then the left eye, and Session 2, ERGs were recorded from the left eye then the right eye. We compared the implicit times, amplitudes and pupil diameters of the right eye between these two sessions.

RESULTS: The implicit time of the flicker ERGs was significantly shorter ($p < 0.001$), and the pupil diameters were significantly smaller ($p = 0.013$) at Session 2 than Session 1 but only for the lower stimulus intensity of eight Td-s. There was a significant correlation of the differences in the implicit times and the differences in the pupil diameter between the two sessions ($r = 0.406$, $p = 0.026$). CONCLUSION: The results indicate that the implicit times of the fundamental components of RETeval flicker ERGs can be affected by the sequence of recordings for lower stimulus intensities. This was most likely due to the differences of the pupil diameter during the recordings. We recommend that stronger stimuli be used to record the RETeval flicker ERGs to minimize the effects of the sequence of recordings.

Man TTC. et al. Evaluation of Electrical Performance and Properties of Electroretinography Electrodes, 2020

PURPOSE: The aim of this study was to evaluate and compare the electrical performance and properties of commercially available electroretinography (ERG) electrodes.

METHODS: A passive ionic model was used to measure impedance, noise, and potential drift in 10 types of ocular surface and skin ERG electrodes.

RESULTS: The impedance for silver-based ocular electrodes are generally lower (range, 65.35–343.3 Ω) with smaller phase angles (range, −6.41° to −33.91°) than gold-based electrodes (impedance ranged from 285.95 Ω to 2.913 kΩ, and phase angle ranged from −59.65° to −70.01°). Silver-based ocular electrodes have less noise (median line noise of 6.48 x 104nV2/Hz) than gold-based electrodes (median line noise of 2.26 x 105nV2/Hz). Although silver-based electrodes usually achieve a drift rate less than 5 µV/s within 15 minutes, gold-base ocular electrode cannot achieve a stable potential. The exception is the RETeval strip type of silver electrode, which had an unusual drift at 20 minutes. The noise spectral density showed no change over time indicating that noise was not dependent on the stabilization of the electrode.

CONCLUSIONS: From the range of electrodes tested, lower impedance, lower capacitance, and lower noise was observed in silver-based electrodes. Stabilization of an electrode is effective against drift of the electrode potential difference but not the noise.

Translational Relevance: Application of electrodes with optimized materials improve the quality of clinical electrophysiology signals and efficiency of the recording.

Jiang & Mahroo O. Negative electroretinograms: genetic and acquired causes, diagnostic approaches and physiological insights, 2021

The dark-adapted human electroretinogram (ERG) response to a standard bright flash includes a negative-going a-wave followed by a positive-going b-wave that crosses the baseline. An electronegative waveform (or negative ERG) results when the b-wave is selectively reduced such that the ERG fails to cross the baseline following the a-wave. In the context of a normally sized a-wave, it indicates a site of retinal dysfunction occurring after phototransduction (commonly at the photoreceptor to bipolar cell synapse). This is an important finding. In genetic disease, the pattern of ERG abnormality can point to variants in a small group of genes (frequently those associated with congenital stationary night blindness and X-linked retinoschisis, but negative ERGs can also be seen in other conditions including syndromic disease). In acquired disease, there are numerous causes, but specific features may point to melanoma-associated retinopathy (MAR). In some cases, the visual symptoms precede the diagnosis of the melanoma and so the ERG findings can initiate investigations facilitating early detection and treatment. Negative ERGs can occur in other paraneoplastic conditions, and in a range of other diseases. This review will outline the physiological basis for the negative ERG, report prevalences in the literature from different cohorts, discuss the range of causes, displaying examples of a number of ERG phenotypes, highlight features of a clinical approach to patients, and briefly discuss further insights relating to current flows shaping the a-wave trough and from single-cell transcriptome analysis.

Chen et al. Qualitative and quantitative comparison of ERGs with contact lens and adhesive skin electrodes, 2022

PURPOSE: Traditional ERGs recorded using corneal electrodes can be difficult for some patients to tolerate. In the last several years, adhesive skin electrodes have gained in acceptance. In this report we present a qualitative comparison of waveforms as well as a quantitative analysis of correlation of amplitudes and implicit times of simultaneous ERG recordings using contact lens and skin electrodes.

METHODS: 89 subjects were included; all were referred for full-field ERG testing for multiple indications. ERGs (obtained according to ISCEV standards) were recorded simultaneously from both eyes with ERG-jet corneal contact lens electrodes and LKC Technologies Sensor Strip adhesive skin electrodes using multi-channel instrumentation (Diagnosys LLC, Espion3). Waveforms, a-wave and b-wave amplitudes and implicit times were compared.

RESULTS: Waveform morphologies were similar between electrode types. Regression coefficients (conversion factors) for a-wave and b-wave amplitudes under both photopic and scotopic conditions were tightly clustered. Regression coefficients for implicit times were nearly equal to 1.0. The regression coefficient for the entire amplitude dataset was 0.349, with an overall correlation of 0. 869 between amplitude recorded with skin and contact lens electrodes. The regression coefficient for the entire implicit time dataset was 0.967, with an overall correlation of 0.964 between skin and contact lens electrodes.

CONCLUSION: Our best estimate for the conversion factor between ERG amplitudes recorded with adhesive skin electrodes and contact lens electrodes is 0.349—amplitudes with skin electrodes are about 1/3 the amplitudes recorded simultaneously from the same eyes with contact lens electrodes, with a high correlation. Implicit times are nearly identical for the two electrode types.

Song et al. Current usage of electrophysiological tests in a secondary referral hospital in Korea, 2022

PURPOSE: To investigate the current status of electrophysiological test use in ophthalmology.

METHODS: We analyzed 1057 electrophysiological tests conducted at Kim's Eye Hospital from January 1 to December 31, 2018. The included tests were electroretinogram (full-field, multifocal, and pattern ERG), electrooculogram (EOG), and visual evoked potential (pattern and flash VEP). To investigate the distribution of use of subspecialties, it was divided by subspecialties (retina, glaucoma, oculoplastic surgery, pediatric ophthalmology, neuro-ophthalmology, cornea, and external diseases).

RESULTS: The patients were aged 50.6 years on average and included 624 men and 433 women. Among the electrophysiological tests, VEP was the most common, with 567 cases (53.6%), followed by ERG with 311 cases (29.4%) and EOG with 98 cases (9.3%). Regarding the purpose of use, the objective of visual function evaluation was the highest at 56.3%, followed by the differential diagnosis of unknown causes (33.0%) and the confirmation of diagnoses (10.7%). Both VEP and ERG were used the most for visual function evaluation, and mfERG was most used for differential diagnosis of unknown etiology. Electrophysiological tests were

most often used in the retina department, but VEPs were used in various fields such as neuro-ophthalmology, glaucoma, and oculoplastics.

CONCLUSION: Electrophysiological tests are used to objectively evaluate visual function or discriminate diseases of unknown causes and are used in various departments. Electrophysiology testing is expected to be an additional test to assess visual function.

Asakawa et al. Pupil assessment with a new handheld pupillometer in healthy subjects, 2022

OBJECTIVE: To assess the pupil response with a new handheld pupillometer in healthy subjects.

METHODS: Sixty-four eyes of 32 healthy subjects (mean age 21.2 years) were tested. After dark adaptation for 10 min, pupil responses to 1 s red and blue light stimuli at 100 cd/m2 were measured in the order from right to left eyes with a 1 min interval. The initial pupil size (D1, mm), minimum pupil size (D2, mm), and constriction rate (CR, %) were obtained. Intra-examiner reproducibility was examined using the coefficient of variation (CV, %) and the Bland–Altman plot. Inter-examiner consistency was examined using the interclass correlation coefficient (ICC) and the agreements with a conventional device, by Pearson's correlation coefficient (r).

RESULTS: The CV of all parameters have high reproducibility in the red (11.0–20.7%) and blue (5.5–12.1%) light stimuli. Bland–Altman plot analysis showed no bias with both light stimuli. "Almost perfect" and "substantial" correlations between the examiners were obtained in the red (ICC = 0.78–0.94) and blue (ICC = 0.71–0.89) light stimuli. "Excellent" and "good" correlations between the devices were obtained, except for the CR parameter in the red (D1: $r = 0.90$; $p < 0.001$, D2: 0.72; $p < 0.001$, and CR: 0.08; $p = 0.631$, respectively) and blue (D1: $r = 0.87$; $p < 0.001$, D2: 0.70; $p < 0.001$, and CR: 0.19; $p = 0.274$, respectively) light stimuli.

CONCLUSION: The novel pupillometer is useful for assessing pupil response. However, because of their different constructions, the CR values cannot be compared directly between the devices.

Mahroo et al. Visual electrophysiology and "the potential of the potentials", 2023

Visual electrophysiology affords direct, quantitative, objective assessment of visual pathway function at different levels, and thus yields information complementary to, and not necessarily obtainable from, imaging or psychophysical testing. The tests available, and their indications, have evolved, with many advances, both in technology and in our understanding of the neural basis of the waveforms, now facilitating more precise evaluation of physiology and pathophysiology. After summarising the visual pathway and current standard clinical testing methods, this review discusses, non-exhaustively, several developments, focusing particularly on human electroretinogram recordings. These include new devices (portable, non-mydiatric, multimodal), novel testing protocols (including those aiming to separate rod-driven and cone-driven responses, and to monitor retinal adaptation), and developments in methods of analysis, including use of modelling and machine learning. It is likely that several tests will become more accessible and useful in both clinical and research settings. In future, these methods will further aid our understanding of common and rare eye disease, will help in assessing novel therapies, and will potentially yield information relevant to neurological and neuro-psychiatric conditions.

Saad, A. The Use of the RETeval Portable Electroretinography Device for Low-Cost Screening: A Mini-Review, 2024

Electroretinography (ERG) provides crucial insights into retinal function and the integrity of the visual pathways. However, ERG assessments classically require a complicated technical background with costly equipment. In addition, the placement of corneal or conjunctival electrodes is not always tolerated by the patients, which restricts the measurement for pediatric evaluations. In this short review, we give an overview of the use of the RETeval portable ERG device (LKC Technologies, Inc., Gaithersburg, MD, USA), a modern portable ERG device that can facilitate screening for diseases involving the retina and the optic nerve. We also review its potential to provide ocular biomarkers in systemic pathologies, such as Alzheimer's disease and central nervous system alterations, within the framework of oculomics.

Kozaki, T. Effect of Diurnal Light Conditions on Electroretinogram Responses to Red and Blue Flickering Light, 2024

Bright light impacts the human circadian system such that exposure to bright light at night can suppress melatonin secretion, and exposure to bright light in the morning prevents light-induced melatonin suppression at night. The preventive effect of morning light may attenuate the prior history of light sensitivity of intrinsically photosensitive retinal ganglion cells (ipRGCs) that regulate the circadian system. In this study, we evaluated electroretinogram (ERG) responses to red and blue flickering lights following dim and bright daylight conditions. Eleven healthy females underwent ERG measurements during exposure to 33 Hz flickering red or blue light under dim and bright daytime conditions. We averaged ERG waves for 50 flickering light pulses of the trigger signal data. We obtained the amplitude of the signal-averaged ERG by calculating the difference between the waves' peaks and bottoms. Although there was no significant dim and bright light difference in the amplitude of ERG waves, the ERG amplitude to flickering blue light under the bright light condition was significantly lower than to flickering blue light under the dim light condition. In this study, blue light stimulated mainly ipRGCs and S-cones. Since S-cones may contribute minimally to the light-adapted 33 Hz flicker ERG results, our findings suggest that bright light during the daytime attenuates the sensitivity of human ipRGCs.

Bayer, S. Could a hand-held, visual electrophysiology device theoretically reduce diagnostic waiting times for complex eye conditions in the NHS? A Discrete Event Simulation (DES) modelling study, 2025

BACKGROUND/OBJECTIVES Visual Electro-Diagnostic Testing (EDTs) are a highly specialised service in the NHS. The high cost of tests and a paucity of trained visual electrophysiologists has resulted in very few services across the UK and, when combined with increasing patient backlogs, has caused significant travel burden and variable waiting times. Here, we study the potential for impact on patients and services by adding a screening step to traditional referral pathways using an Electroretinogram (ERG) test from a relatively inexpensive, portable, hand-held EDT device; the RETeval® (LKC technologies, Gaithersburg, MD, USA).
SUBJECTS/METHODS We model a large regional-referral EDT service using Discrete Event Simulation (DES) modelling based on retrospective patient data and published best evidence for the device. We evaluate the potential impact that adding the screening step in referral pathways could have on patient waiting times should the device prove to be safe and useable in clinical practice. **RESULTS** We demonstrate that should the RETeval® ERG be safe and useable in real-world clinical practice, it has the potential to significantly reduce patient waiting times by avoiding lab-based EDT assessment for up to 45% of patients. We also show that the impact on services and patients is likely to be resilient to realistic changes in referral numbers, sensitivity/specificity of the device and changes in clinical capacity.
CONCLUSIONS This work demonstrates that a RETeval® ERG screening step, performed at the point of referral, has the potential to result in significantly reduced EDT waiting lists through fewer patients requiring lab-based EDT assessment and that DES modelling is a useful tool in making this assessment. However, many questions remain about using the device in the real-world setting for this purpose. Future studies are needed to assess its sensitivity/ specificity, test/retest variability, changes in referral patterns due to the device, useability, acceptability to patients and importantly, the consequences of screening errors. Our work, using only retrospective data and a DES model, shows that using the device as an ERG screening tool warrants further investigation due to the potential impact on both patients and clinical services

Kulyabin, M. Synthetic electroretinogram signal generation using a conditional generative adversarial network, 2025

BACKGROUND**:** he electroretinogram (ERG) records the functional response of the retina. In some neurological conditions, the ERG waveform may be altered and could support biomarker discovery. In heterogeneous or rare populations, where either large data sets or the availability of data may be a challenge, synthetic signals with Artificial Intelligence (AI) may help to mitigate against these factors to support classification models.
METHODS**:** This approach was tested using a publicly available dataset of real ERGs, n = 560 (ASD) and n = 498 (Control) recorded at 9 differ ent flash strengths from n = 18 ASD (mean age 12.2 ± 2.7 years) and n = 31 Controls (mean age 11.8 ± 3.3 years) that were augmented with synthetic waveforms, generated through a Conditional Generative Adversarial Network. Two deep learning models were used to classify the groups using either the real only or combined real and synthetic ERGs. One was a Time Series Transformer (with waveforms in their original form) and the second was a Visual Transformer model utilizing images of the wavelets derived from a Continuous Wavelet Transform of the ERGs. Model performance at classifying the groups was evaluated with Balanced Accuracy (BA) as the main outcome measure.

RESULTS: The BA improved from 0.756 to 0.879 when synthetic ERGs were included across all recordings for the training of the Time Series Transformer. This model also achieved the best performance with a BA of 0.89 using real and synthetic waveforms from a single flash strength of 0.95 log cd s m−2.
CONCLUSIONS: The improved performance of the deep learning models with synthetic waveforms supports the application of AI to improve group classification with ERG recordings.

Kato, K. Minimizing Pupil Size Dependence in Flicker ERG Using Stiles–Crawford Compensation, 2025

PURPOSE: This study determined the impact of the Stiles–Crawford effect (SCE) on electroretinograms (ERGs). Compensating for the SCE can improve the diagnostic reliability of ERGs by providing a stimulus minimally affected by pupil size.
METHODS: Flicker ERGs were recorded from 10 healthy subjects at 3-minute intervals over 21 minutes after mydriasis. The RETeval system adjusted retinal illuminance in real time based on pupil size measurements, using a Troland stimulus and preset SCE compensation factors (ρdevice) of 0, 0.05, 0.085, and 0.12 mm−2.
RESULTS: Larger pupil areas led to prolonged implicit times with ρdevice = 0and 0.05 mm−2, whereas ρdevice = 0.12 mm−2 reduced implicit time. Amplitudes were lower with ρdevice = 0mm−2 but increased with ρdevice = 0.085 and 0.12 mm−2.Thevalues that minimized pupil size dependence were ρdevice = 0.086 mm−2 for the implicit time of the fundamental component of the ERG and ρdevice = 0.05 mm−2 for all other measures. Variability in ERGs based on pupil size is predicted to be ≤7% of the associated 95% reference interval for Troland stimuli over the range of nonmydriatic pupil sizes, compared to ≤43% for luminance stimuli over the range of mydriatic pupil sizes.
CONCLUSIONS: Using Troland stimuli with ρdevice = 0.05 mm−2 for all cone-mediated ERGs would minimize the impact of pupil size, although the improvement would be modest for ERGs performed with Troland stimulation without SCE compensation on non-dilated subjects.

Yoshiaki, C. Light-adapted electroretinograms of eyes with cataract recorded using the HE-2000 system before and after mydriasis, 2025

To evaluate the effectiveness of the non-mydriatic mode of the HE-2000 electroretinogram (ERG) by comparing photopic ERGs of non-mydriatic versus dilated eyes. This retrospective study included patients with grade 2 cataracts between January and July 2022. Photopic ERGs were recorded using the HE-2000 system in mydriatic eyes with a 3 cd·s/m2 flashing stimulus and in non-mydriatic eyes using the non-mydriatic mode with a 10 cd·s/m2 stimulus. Amplitudes and implicit times of the a-wave, b-wave, and flicker ERG were compared using the Wilcoxon signed-rank test. Correlations between these parameters were analyzed using Spearman's rank correlation coefficient. In 54 eyes of 27 participants, the b-wave and flicker ERG amplitudes were lower in non-dilated eyes compared to dilated ones, with prolonged implicit times observed in non-dilated eyes ($p < 0.0001$). Despite these differences, both b-wave and flicker ERG amplitudes and implicit times showed strong correlations between dilated and non-dilated eyes ($p < 0.01$). However, the a-wave amplitude was more variable and less consistently measurable in non-dilated eyes. The HE-2000 system can provide clinically useful ERG recordings in non-dilated eyes, particularly for b-wave and flicker responses. Further validation under non-mydriatic conditions is required to establish its broader clinical utility.

Tyler, C. Native components analysis of the spectral electroretinogram, 2025

The electroretinogram (ERG) is a mass electrical response from all electrically activated components of the retina, recorded with the goal of identifying the individual contributions of relevant components for the purposes of electrodiagnosis of eye diseases and other systemic medical conditions. The primary hypothesis being tested was that the ERGs across the spectrum in the mesopic range of intensities could be fully accounted with a duplex (two-component) model of linear combinations of rod- and cone-pathway responses. Full-field square-wave ERGs were measured with the RETeval device at 2 Hz for 7 spectral bands: red, yellow, green, cyan, blue, magenta, and white, in increasing steps of 0.5 log units from 3 to 300 phot cd/m2, totaling 35 conditions for each eye of three neurotypical participants. A novel three-stage process termed Native Components Analysis (NCA), designed to overcome the distributive and orthogonality disadvantages of conventional linear component analysis, was implemented to identify the components contributing to the On-response of the overall ERG. The first step was select the ERG waveforms representative of each region of the response matrix. They were thus designated in terms of a) high and low intensities and b) the narrowband red, green and blue spectral regions. These 6 waveforms were taken as the native component candidates for an optimized fit to the full dataset. The second step was to determine the fit of these ERG components so-defined to the overall set of recorded ERG On-responses from each eye – a

140-parameter fit to the 10,500-parameter dataset. This approach was then compared with the standard approach of orthogonal Principal Components Analysis (PCA) to provide comparable compression. Over 6 datasets from the two eyes of three participants, the fit of the first 4 factors of the novel NCA approach accounted for 95.0 % of the overall variance in the data, compared with 97.5 % for the standard PCA approach. Adding components beyond the best 4 provided no significant improvement in the fits. For the individual datasets, the fit of the PCA accounted for 95.4 – 99.1 % of the variance, while the fit of the representative ERGs of the NCA approach accounted for 89.6–98.1 % of the variance across the individual datasets, validating the strategy of using representative ERG responses as the analytic components. The NCA fits strongly disconfirm the duplex rod/cone model that the ERG is a combination of just two temporal components, showing that as many as four separate components are required to account for the variance in the 35 waveforms in the participant group, with consistent structure across the spectral datasets. These results validate the utility of the novel Native Components Analysis approach to functional response analysis of retinal signals.

Sommer, C. The reproducibility of handheld ERGs recorded with skin electrode and natural pupils, 2025

PURPOSE To investigate the reproducibility of handheld full-field electroretinogram (ERG) to determine the minimum change required in longitudinal measurements to reach statistical significance.
METHODS The study included 27 healthy volunteers, aged 45–65. Light-adapted (ISCEV standard) full-field ERGs measured with the RETeval device (LKC Technologies, Germantown, MD, USA) were recorded using non-invasive skin electrodes, followed by a second examination 1–14 days later. Intersession variability of the a- and b-waves, the flicker responses (light intensity 85 Td·s, frequency 28.3 Hz) and the photopic negative response (PhNR, 38 Td·s on 380 Td blue) were assessed.
RESULTS The mean standard deviations were 0.86, 0.83, 0.40 and 3.24 ms for a-wave, b-wave, flicker and PhNR peak times, respectively. Coefficient of variations (CV) were 32%, 22%, 18%, and 19.2% for the amplitudes of the a-wave, b-wave, flicker and PhNR, respectively.
CONCLUSION While flicker ERGs had the smallest variability, ISCEV standard a-wave and b-wave times also had variability less than 1 ms, indicating excellent reproducibility. Amplitudes were more variable, with the a-wave amplitude having the most variability. While it depends on disease, longitudinal studies utilizing ERG timing are expected to be more likely to show statistically significant results due to low inter-session variability.

Park, J. A rapid pupillometry protocol for clinical use: effect of age and test–retest repeatability, 2025

PURPOSE Pupillometry is most commonly performed in laboratory settings using specialized, non-portable instruments that require lengthy test protocols. The purpose of this study was to develop and evaluate a rapid, clinically-applicable pupillometry protocol using a commercially available, portable, handheld instrument.
METHODS Thirty-seven healthy individuals (ages 21–61 years) participated in three experiments. In each experiment, the pupillary light reflex (PLR) was elicited by full-field, 500 ms chromatic flashes (470 nm and 621 nm; 12,000 Td). Experiment I evaluated the minimum dark adaptation (DA) time needed to achieve maximum PLRs. Experiment II determined the effect of age. Experiment III estimated PLR test–retest repeatability. For all experiments, baseline pupil size (BL; 1 s before flash onset), maximum pupil constriction (MPC) following the flash, and post-illumination pupillary response (PIPR; median size 6–8 s after flash offset) were quantified.
RESULTS Experiment I showed that from 1 to 3 min of DA, BL and MPC increased slightly (0.27 mm and 5%, respectively), whereas the PIPR increased considerably (17%). The responses did not change appreciably after 3 min, therefore a 3 min DA period was used for Experiments II and III. Experiment II showed a trend for BL and MPC to decrease with age, but correlations with age were not statistically significant (all $p > 0.05$). PIPR was independent of age ($r = -0.01$; $p = 0.96$). Experiment III showed test–retest repeatability of approximately 1 mm for BL, and 10% for MPC and PIPR, indicating good repeatability.
CONCLUSION The proposed approach is useful for measuring the MPC and PIPR across a broad range of ages and baseline pupil sizes. Given the device portability and short test duration (approximately 5 min including DA), this approach has promising clinical utility.

Chiku, Y. Light-adapted electroretinograms of eyes with cataract recorded using the HE-2000 system before and after mydriasis, 2025

To evaluate the effectiveness of the non-mydriatic mode of the HE-2000 electroretinogram (ERG) by comparing photopic ERGs of non-mydriatic versus dilated eyes. This retrospective study included patients with grade 2 cataracts between January and July 2022. Photopic ERGs were recorded using the HE-2000 system in mydriatic eyes with a 3 cd·s/m2 flashing stimulus and in non-mydriatic eyes using the non-mydriatic mode with a 10 cd·s/m2 stimulus. Amplitudes and implicit times of the a-wave, b-wave, and flicker ERG were compared using the Wilcoxon signed-rank test. Correlations between these parameters were analyzed using Spearman's rank correlation coefficient. In 54 eyes of 27 participants, the b-wave and flicker ERG amplitudes were lower in non-dilated eyes compared to dilated ones, with prolonged implicit times observed in non-dilated eyes ($p < 0.0001$). Despite these differences, both b-wave and flicker ERG amplitudes and implicit times showed strong correlations between dilated and non-dilated eyes ($p < 0.01$). However, the a-wave amplitude was more variable and less consistently measurable in non-dilated eyes. The HE-2000 system can provide clinically useful ERG recordings in non-dilated eyes, particularly for b-wave and flicker responses. Further validation under non-mydriatic conditions is required to establish its broader clinical utility.

Arias-Alvarez, M. The Mydriasis-Free Handheld ERG Device and Its Utility in Clinical Practice: A Review, 2026

BACKGROUND: Full field electroretinography (ERG) is an essential tool for assessing retinal function and diagnosing retinal diseases. In recent years, mydriasis-free handheld ERG devices have emerged as portable, non-invasive alternatives to traditional ERG systems. Their main application has been in the screening and monitoring of diabetic retinopathy (DR), particularly in settings with limited access to standard ERG equipment and in pediatric populations where conventional testing may be difficult to perform. This review aims to evaluate the current evidence on handheld ERG devices in ocular diseases, with a focus on their reliability, diagnostic accuracy, and inherent limitations.
METHODS: A review was conducted to identify studies evaluating handheld ERG devices in diverse clinical settings, including retinal diseases, DR, pediatric populations, and conditions such as glaucoma. A comprehensive search of the Pubmed and Embase databases was performed for studies published up to December 2024. Search terms included "mydriasis free ERG", "handheld ERG", "portable ERG", "RETeval", "healthy subjects", "retinal diseases", "diabetic retinopathy", "glaucoma", and "pediatric diseases", as well as relevant MeSH terms and synonyms. Case reports, conference abstracts, non-human studies, and letters were excluded. After screening titles and abstracts, additional studies not meeting the inclusion criteria were excluded. Of 279 records that were initially identified, 55 met the eligibility criteria and were included in the final review. Results were synthesized narratively due to heterogeneity in the study design, populations, and outcomes. Findings were organized thematically according to clinical context.
RESULTS: A total of 57 studies were included in the review: 19 conducted in healthy subjects, 13 in diabetic retinopathy, eight in selected retinopathies, eight in glaucoma, and 14 in pediatric cohorts. Five studies overlapped between groups due to shared populations or study designs. No meta-analysis was performed due to heterogeneity in study design and outcome measures; therefore, findings were summarized narratively across disease categories. Handheld ERG devices have been evaluated in healthy subjects, patients with DR, other retinal pathologies, glaucoma and pediatric cohorts. Evidence indicates that these devices provide a rapid, non-invasive assessment of retinal function and are particularly valuable where conventional ERG is difficult to implement and potentially well-suited for screening purposes. They show good sensitivity and reasonable specificity for detecting functional changes, making them suitable for screening purposes. However, limitations exist: reduced performance in detecting early-stage disease and cone dysfunction, risk of false positives, and variability in waveform morphology and amplitude compared with traditional ERG systems. Reproducibility challenges are noted among pediatric patients and individuals with poor fixation or unstable eye movements. These discrepancies highlight the need for establishing robust normative datasets for both healthy subjects and specific disease states.
CONCLUSIONS: Handheld ERG devices provide a rapid, accessible and user-friendly option for retinal assessment. While not a replacement for conventional ERG, they serve as complementary tools, particularly in early disease and in contexts where standard testing is less feasible. Further research is required to refine testing protocols, improve diagnostic accuracy, and validate their application across a broader spectrum of ocular diseases.

Brabec, M. Technical Note: Contour Plot Visualization of the Light Adapted Electroretinogram Using a Generalized Additive Model, 2026

PURPOSE To describe a new method to visualize the amplitude profile of light adapted ERGs as a series of contour plots in response to a Flash Strength series.

METHODS Light adapted ERGs from a dataset of n = 88 Autism Spectrum Disorder (ASD) and n = 70 typically developing Control participants were used incorporating 10 flash strengths ranging from 12 to 446 Troland seconds (Td.s). The region chosen for analysis included the baseline, a-wave and ascending limb of the b-wave and included n = 1736 control and n = 1300 ASD waveforms. A Generalized Additive Model (GAM) with complexity penalized tensor product splines was applied to the waveform intervals.

RESULTS Contour plots derived from the ASD and Control groups revealed a pattern of reduced amplitude in the ascending limb of the b-wave for the ASD group. Representative responses were derived from the GAM model for discrete Flash Strengths to exemplify the changing profile of the ERG waveform. A contour plot of the derived z-scores provided a qualitative evaluation of the differences in the mean amplitudes which was concentrated on the b-wave.

CONCLUSIONS The production of contour plots based on amplitude, time and Flash Strength with minimal a priori assumptions provide an additional approach to analyzing stimulus response data series and may support clinical applications. Additionally, the GAM-based methodology provides a tool for simultaneous investigation of the amplitude changes over time and Flash Strength which can be useful for theoretical purposes.

Reference Data Publications

Soekamto, C. Using the RETeval Device in Healthy Children to Establish Normative Electroretinogram Values, 2021

PURPOSE: To provide normative data of full-field electro-retinogram (ERG) responses in the pediatric population using the RETeval ERG device (LKC Technologies, Inc) in healthy children without evidence of retinal disease.

METHODS: This was a single-site cross-sectional study of healthy pediatric patients with normal dilated fundus examinations and no known retinal diseases. Participants were recruited to undergo dilated full-field ERG using the handheld RETeval device. The International Society for Clinical Electrophysiology of Vision 5-step protocol was used. Photopic and dark-adapted scotopic responses were recorded using skin electrodes.

RESULTS: Main outcome measures were normative RETeval ERG values and correlation of age with measured ERG parameters. Thirty-eight eyes of 20 healthy patients (aged 4 to 17 years) were included in the study. Of the 20 normal patients, 9 were male and 11 were female. Normative mean, median, and range values were recorded for the measured full-field ERG parameters. Pearson correlation was moderately positive between age and oscillatory potential and scotopic dim flash amplitude ($r = 0.59$, $P = .006$ for both). A positive correlation was also found between age and cone a-wave implicit time ($r = 0.67$, $P = .001$).

CONCLUSIONS: The handheld RETeval system is a useful tool for obtaining full-field ERGs in children without anesthesia. Moderate positive correlations were observed between age and oscillatory potential and scotopic dim flash amplitude. A strong correlation was found between age and cone a-wave implicit time. The current study provides a baseline of normative full-field ERG values in children.

Zhang, T. Mydriasis-Free Flicker Electroretinograms in 204 Healthy Children Aged 0–18 Years: Reference Data From Two Cohorts, 2021

PURPOSE: The purpose of this study was to summarize the flicker electroretinogram responses (ERGs) in healthy children using RETeval, a small handheld mydriasis-free fullfield flicker ERG system.

METHODS: Flicker ERGs were recorded with the use of the RETeval systemin 204 healthy children (aged 18 years and below) from 2 countries, China and the United States. The effects on ERG measurements of the subject's demographics and location were analyzed.

RESULTS: The implicit times have no correlation with the population (China cohort and US cohort), sex, and refractive error. In contrast, the amplitudes were dependent on demographics. The amplitude differences were small compared to the 95% reference interval; therefore, a single (age-corrected) reference interval can be used in both locations and both sexes. The implicit times and amplitudes mature over the first decade of life with exponential time constants of 2.5 years and 4.1 years, respectively, whereas most of the trend is within the first 6 years (implicit times) and 9 years (amplitudes).

CONCLUSIONS: The age dependence and percentiles obtained in this study could serve as reference data against which the ERG responses from pediatric patients can be compared.

TRANSLATIONAL RELEVANCE: The flicker ERG is one of the standard methods for the assessment and diagnosis of vision-related disorders. This study provides reference data in pediatric subjects, which can then be used to aid in the interpretation of flicker ERG results.

Zhang et al. The Development of Electroretinographic Oscillatory Potentials in Healthy Young Children, 2022

ABSTRACT: Purpose: This study aimed to summarize the electroretinographic oscillatory potential (OP) responses in healthy young children recorded by RETeval.

METHODS: By using the RETeval system, we recorded the implicit times and amplitudes of the OPs (OP1-5), in 132 healthy children aged from 0 to 11 years old. The age, gender, and data of implicit time and amplitude of each child were recorded and analyzed. Correlation analysis was performed between age and implicit time/amplitude.

RESULTS: No correlation was shown between the implicit times and amplitudes with gender. The implicit times and amplitudes of OP1-5 matured over 10 years of age, with exponential time constants of 1.9, 2.2, 1.8, 1.7, and 1.6 years and 2.1, 2.9, 2.8, 3.0, and 3.2 years, respectively. The majority of the trend occurred within the first 4.6 years.

CONCLUSIONS: In order to diagnose and evaluate vision-related disorders, the OP response is commonly used. The percentiles and age dependence of OP responses calculated and shown in this study could be regarded as reference data in age-matched pediatric patients.

Inooka et al. Assessment of factors affecting flicker ERGs recorded with RETeval from data obtained from health checkup screening, 2023

PURPOSE: To determine the factors significantly associated with the amplitudes and implicit times of the flicker electroretinograms (ERGs) recorded with the RETeval system by analyzing the comprehensive data obtained during a health checkup screening.

METHODS: Flicker ERGs were recorded with the RETeval system from 373 individuals who had a normal fundus and optical coherence tomography images. The sex, age, anthropometric, ophthalmologic, and hematologic data were collected from all participants who were 40- to 89-years-of-age. Univariable and multivariable linear mixed effects regression analyses were performed to identify factors that were significantly associated with the implicit times and amplitudes of the RETeval flicker ERGs.

RESULTS: Univariable linear mixed effects regression analysis showed significant correlations between the implicit times and the best-corrected visual acuity, the age, the axial length, the blood sugar level, and the blood urea nitrogen level. Analyses by multivariable linear mixed effects regression identified that the axial length (β = 0.28), the age (β = 0.24), and the blood sugar level (β = 0.092) were three independent factors that were significantly correlated with the implicit times of the RETeval flicker ERGs. Univariable linear mixed effects regression analysis also showed significant correlations between the amplitudes of the RETeval flicker ERGs and the age, the platelet count, and the creatinine level. Multivariable linear mixed effects regression models identified the age (β = -0.092), the platelet count (β = 0.099), and the creatinine level (β = -0.12) as three independent factors that were significantly correlated with the amplitudes of the RETeval flicker ERGs. However, the smoking habits, body mass index, and the blood pressure were not significantly correlated with either the implicit times or amplitudes of the RETeval flicker ERGs.

CONCLUSIONS: Our results indicate that the age and some ophthalmologic and hematologic findings but not the anthropometric findings were significantly associated with the implicit times and amplitudes of the RETeval flicker ERGs. Thus, clinicians should remember these factors when analyzing the RETeval flicker ERGs.

Chan, S. Paediatric norms for photopic electroretinogram testing based on a large cohort of Chinese preschool children, 2024

OBJECTIVE: Full-field electroretinogram (ffERG) is an objective test to determine the electroretinal activities in response to light stimulation for investigating retinal physiology and diagnosing retinal diseases. This study aimed to establish a reference data set of photopic electroretinogram (ERG) of Chinese preschool children in Hong Kong to facilitate clinical and research studies.

METHODS: Preschool children aged 3–7 years with normal vision were recruited from local kindergartens. Eye examinations, including cycloplegic spherical equivalent refraction (SER), axial length (AL) and keratometry (K) measurements, were performed. ffERGs of the International Society for Clinical Electrophysiology of Vision (ISCEV) standard photopic flash and 30-Hz flicker protocols were measured using RETeval with Sensor Strip skin electrodes. ERG waveform characteristics were extracted, and relationships between ERG, age, SER, AL and K were evaluated.

RESULTS: A total of 479 children completed the measurements (mean age: 5.0±0.9 years, 45.5% female). Mean, 95% CIs, 5th–95th percentile range of the ERG parameters were reported. Age was positively associated with amplitudes of b-wave and 30-Hz flicker ($p<0.01$), but negatively associated with implicit times of b-wave and 30-Hz flicker ($p<0.01$). AL was significantly associated with all amplitudes of a-wave, b-wave and 30-Hz flicker ($p\leq0.01$) and implicit time of both a-wave and 30-Hz flicker ($p<0.05$). K was positively associated only with 30Hz flicker amplitude ($p=0.01$), and no association between all responses and SER.

CONCLUSION: Reference data set of photopic ERG of Chinese preschool children was established. Crosssectional investigations revealed associations between ERG, age, SER and AL, which were speculated to further implicate the role of retina in refractive error development.

Chan, S. Reference ranges of light-adapted full-field electroretinogram and associated factors in a large cohort of healthy school-aged children and adolescents, 2025

PURPOSE: This study aimed to establish a reference data set of light-adapted full-field electroretinograms (ffERG) of healthy primary and secondary schoolchildren and investigate the relationship among refraction, ocular biometry, and ffERG.

METHODS: Healthy children aged between 6 and 17 years were recruited. Cycloplegic spherical equivalent refraction (SER), axial length (AL) and keratometry (K) measurements were performed. Standardized ffERGs, including light-adapted flash and 30-Hz flicker, were measured using a portable device with skin electrodes. The percentiles of peak time and amplitude of a- and b-waves and 30-Hz flicker of ffERG waveform were reported, and their relationships with age, SER, AL, K were investigated.

RESULTS: Among the 445 participants (45.4% female), the SER (mean ± standard deviation) was −0.72 ± 2.06 D and AL was 23.56 ± 1.15 mm. The 90% confidence interval (CI) of 5th reference limit of amplitudes of a- and b-wave were 5.0–5.8 μV and 15.0–17.6 μV, while 95th reference limit of peak times were 13.2–13.4 ms and 29.8–30.0 ms, respectively. The amplitude and peak time of the 30-Hz flicker waveform were 21.5–23.9 μV and 26.0–26.2 ms, respectively. In general, more myopic SER, and longer AL were associated with delayed and reduced ffERG waveforms. Older age and male sex were weakly correlated with ffERGs with minimal clinical significance.

CONCLUSIONS: A reference data set of light-adapted ffERG in children and adolescents was established for clinical and research purposes.

Diabetic Retinopathy

Fukuo M. et al. Screening for diabetic retinopathy using new mydriasis-free, full-field flicker ERG recording device, 2016

PURPOSE: The purpose of this study was to determine whether a small, hand-held, mydriasis-free, full-field flicker electroretinographic (ERGs) device called RETeval can be used to screen for DR.

METHOD: This was a prospective, cross sectional, single-center study,(…). One hundred and eighteen eyes of 118 patients with DM and 48 eyes from 48 normal subjects were studied. The results of only the right eye were used for the statistical analyses. (…) we recorded full-field flicker ERGs with this device from 48 normal eyes and 118 eyes with different severities of DR in patients with diabetes mellitus (DM).

All of the patients with DM had comprehensive ocular examinations including measurements of the best-corrected visual acuity (BCVA), refractive error by autorefractometry, and intraocular pressure (IOP) with a non-contact tonometer. In addition, they had anterior segment examination by slit-lamp biomicroscopy. After mydriasis, fundus examinations were performed by indirect ophthalmoscopy, and color fundus photographs were recorded.

RESULTS/CONCLUSION: Our results showed that there were significant correlations between the severity of DR and the implicit times ($P < 0.001$; $r = 0.55$) and the amplitudes ($P = 0.001$; $r = -0.29$).

These results suggest that the implicit times of the flicker ERGs recorded by the small, mydryasis-free ERG system can be used as an adjunctive tool to screen for DR.

Maa A.Y. et al. A novel device for accurate and efficient testing for vision-threatening diabetic retinopathy, 2016

PURPOSE: To evaluate the performance of the RETeval device, a handheld instrument using flicker electroretinography (ERG) and pupillography on undilated subjects with diabetes, to detect vision-threatening diabetic retinopathy (VTDR).

METHOD: Performance was measured using a cross-sectional, single armed, non-interventional, multi-site study with Early Treatment Diabetic Retinopathy Study 7-standard field, stereo, color fundus photography as the gold standard. The 468 subjects were randomized to a calibration phase (80%), and a validation phase (20%).

RESULTS/CONCLUSION: With a sensitivity of 83%, the specificity was 78% and the negative predictive value was 99%. The average testing time was 2.3 min. (…) the RETeval device will identify about 75% of the population as not having VTDR with 99% accuracy. The device is simple to use, does not require pupil dilation, and has a short testing time.

Al-Otaibi M. et al. Validity, Usefulness and Cost of RETeval System for Diabetic Retinopathy Screening, 2017

PURPOSE: The purpose of our study was to evaluate the RETeval as a screening tool in (sight-threatening) DR compared to conventional digital retinal photographs. We further evaluated the ease of use and cost-effectiveness of DR screening using RETeval.

METHOD: Patients with diabetes attending the screening unit of King Khaled Eye Specialist Hospital, Riyadh, Saudi Arabia were evaluated by "RETeval", Amsler grid, and digital dilated fundus photography. Fundus images were evaluated by a retina specialist to determine grade of DR. The sensitivity and specificity of STDR and DR screening compared to photography were calculated, as well as "RETeval" combined with Amsler grid testing.

RESULTS/CONCLUSION: RETeval is a rapid screening device with excellent sensitivity for detecting STDR. It has potential as a first level screening tool to detect patients who require further evaluation.

Degirmenci M.F.K. et al. Role of a mydriasis-free, full-field flicker ERG device in the detection of diabetic retinopathy, 2018

PURPOSE: To determine if the RETeval system can be used for the screening of diabetic retinopathy (DR) to provide early diagnosis.

METHOD: The subjects were 42 diabetic patients selectively recruited by examination of their medical records to have varying severities of DR.

We compared the DR assessment protocol results and the macular RNFL thickness among four groups.

As this study aimed to recognize patients with the risk of progressive DR, the eyes with moderate and severe nonproliferative DR (NPDR) were evaluated as a single group.

RESULTS/CONCLUSION: Our results suggest that the RETeval full-field ERG system can be used as an adjunctive tool for the mass screening of DR, while macular RNFL thickness would not be useful.

Zeng Y. et al. Early retinal neovascular impairment in patients with diabetes without clinically detectable retinopathy, 2019

PURPOSE: To investigate the function and the corresponding neurovascular structures in patients with diabetes and without clinically detectable retinopathy.

METHOD: Sixty-six patients with type 2 diabetes without retinopathy (NOR) and 62 healthy controls were recruited. The 16 and 32 Tds flicker electroretinography (ERG) was performed using a mydriasis-free, full-field flicker ERG recording device (RETeval). The vessel density (VD) of superficial capillary plexus (SCP) and deep capillary plexus (DCP), FD300 and ganglion cell complex (GCC) thickness in the macula were quantified using optical coherence tomography angiography (OCTA). The retinal nerve fibre layer (RNFL) thickness and the radial peripapillary capillary (RPC) density in the peripapillary area were also measured with OCTA.

RESULTS/CONCLUSION: Functional and structural impairments have already started in diabetic retina even in the absence of visible retinal lesions.

After Bonferroni correction, increased implicit time of 16 and 32 Tds light stimuli was significantly correlated with decreased VD of SCP in both parafovea and perifovea regions, and increased implicit time of 32 Tds light stimuli was significantly correlated with VD of DCP in perifovea area.

Zeng Y. et al. Retinal vasculature–function correlation in nonproliferative diabetic retinopathy, 2019

PURPOSE: To compare and correlate retinal microcirculation and function in patients with non-proliferative diabetic retinopathy (NPDR).

METHOD: Thirty-three healthy controls (33 eyes), 36 diabetic patients with no clinically detectable retinopathy (NDR, 36 eyes) and 101 patients (101 eyes) with NPDR (35 mild NPDR, 34 moderate NPDR, 32 severe NPDR) were involved in the study. We used optical coherence tomography angiography (OCTA) to quantify the macular vessel density (VD) of superficial capillary plexus (SCP), deep capillary plexus (DCP) and foveal density in a 300 μm region around foveal avascular zone. Retinal function was assessed by a mydriasis-free, full-field flicker electroretinogram (FERG) recording device, and the amplitudes and implicit time were recorded. The association between microvascular parameters and FERG results was analyzed with stepwise multiple linear regression model.

RESULTS/ CONCLUSION: Decreased amplitudes and delayed implicit time, as well as lower parafoveal/perifoveal VD in both SCP and DCP, were found in NDR group and NPDR groups compared with the control group (all $p<0.05$). Specifically, the FERG parameters and microvascular indices were comparable between NDR group and mild NPDR group (all $p>0.05$). However, compared to mild NPDR, the reduction in FERG amplitude was more pronounced than the reduction in parafoveal VD (both SCP and DCP) in severe NPDR. Stepwise multiple linear regression analyses showed that delayed implicit time was significantly correlated with increased age and decreased VD of parafoveal region in both SCP and DCP in patients with NPDR. Meanwhile, decreased amplitude was significantly associated with decreased VD of parafoveal region in both SCP and DCP in patients with NPDR.

Macular VD in both superficial and deep capillary plexus correlated with ERG implicit time and amplitude in mild-to-severe NPDR. OCTA and FERG may both be useful in detection of preclinical DR and early DR, but once the disease deteriorates, FERG may be more sensitive to discern progression of DR.

Zeng Y. et al. Screening for diabetic retinopathy in diabetic patients with a mydriasis-free, full-field flicker electroretinogram recording device, 2019

PURPOSE: To investigate the accuracy of the RETeval full-field flicker ERG in the screening of diabetic retinopathy (DR) and vision-threatening diabetic retinopathy (VTDR) and to determine a suitable range of DR diagnostic reference for patients with type 2 diabetes mellitus (T2DM).

METHOD: This was a cross-sectional study involving 172 subjects with T2DM, including 71 subjects without clinically detectable DR (NDR), 25 subjects with mild non-proliferative diabetic retinopathy (NPDR), 24 subjects with moderate NPDR, 27 sub-jects with severe NPDR and 25 subjects with proliferative diabetic retinopathy (PDR). All the subjects underwent a full-field flicker ERG using the RETeval device (DR assessment protocol), which is a mydriasis-free, full-field electroretinogram (ERG) recording system. The performance of the DR assessment protocol in detecting the DR (including mild NPDR, moderate NPDR, severe NPDR and PDR) and VTDR was analyzed with the receiver operating characteristic (ROC) curve.

RESULTS/ CONCLUSION: For the detection of DR (mild NPDR, moderate NPDR, severe NPDR, PDR), the area under the ROC curve was 0.867 (p<0.001, 95% CI 0.814–0.920), and the best cutoff value for DR was determined to be 20.75, with a sensitivity of 80.2% and specificity of 81.7%. Meanwhile, for the detection of VTDR, the area under the ROC curve was 0.965 (p<0.001, 95% CI 0.941–0.989), and the best cutoff value was set to 23.05, with a sensitivity of 94.6% and a specificity of 88.8%.

The DR assessment protocol in RETeval device was effective in screening for DR (mild NPDR, moderate NPDR, severe NPDR, PDR) and VTDR in patients with diabetes. It could be helpful in referring and managing patients with T2DM in primary health-care setting. However, caution should be taken that optimal cutoff value of DR assessment protocol may vary in different ethnic populations.

Brigell, M. et al. Enhancing Risk Assessment in Patients with Diabetic Retinopathy by Combining Measures of Retinal Function and Structure, 2020

PURPOSE: To determine whether combining measures of retinal structure and function predicts need for intervention for diabetic retinopathy (DR) better than either modality alone.

METHOD: The study sample consisted of 279 diabetic patients who participated in an earlier cross-sectional study. Patients were excluded if they were previously treated for macular edema or proliferative DR or if they had other retinopathies. Medical records were reviewed for ocular interventions including vitrectomy, intravitreal injection, and laser treatment. Need for intervention was analyzed using Kaplan-Meier analyses and Cox proportional hazards. Baseline electroretinograms and fundus photographs were obtained. Two definitions of structural positive findings were as follows: 1. Early Treatment of Diabetic Retinopathy Study diabetic retinopathy severity scale (ETDRS-DR) severity ≥ level 53 (ETDRS-DR+) and 2. ETDRS-DR+ or clinically significant macular edema (VTDR+). A positive function finding corresponded to a RETeval DR Score >23.5 (RETeval+).

RESULTS/CONCLUSION: For patientswith VTDR+the incidence of intervention was 19%, 31%, and 53% after 1, 2, and 3 years of follow-up. In these patients, intervention incidence increased to 34%, 54%, and 74% the subsequent 1, 2, and 3 years if function was above criterion (RETeval+), whereas RETeval− results reduced the risk to 3%, 4%, and 29%, respectively, reducing risk to similar levels seen for patients with VTDR− results at baseline.

Prediction of subsequent intervention was best when combining structural and functional information.

Kawai, M. et al. Neuroretinal Dysfunction Revealed by a Flicker Electroretinogram Correlated with Peripheral Nerve Dysfunction and Parameters of Atherosclerosis in Patients with Diabetes, 2020

AIMS/ INTRODUCTION: Diabetic polyneuropathy (DPN) develops in the early stage of diabetes. However, no common diagnostic protocol has yet been established. Here, to verify that the flicker electroretinogram using a hand-held device can detect the early dysfunction of the peripheral nervous system in patients with diabetes, we investigated the correlation between the progression of DPN and neuroretinal dysfunction.

METHODS: In total, 184 participants with type 1 or 2 diabetes underwent a flicker electroretinogram (ERG) using a hand-held device RETevalTM and nerve conduction study (NCS). Participants were also evaluated for intima-media thickness (IMT), ankle-brachial index (ABI), toe brachial index (TBI), and brachial-ankle pulse wave velocity (baPWV). Parameters of NCS were used to diagnose the severity according to Baba's classification. A multiple regression analysis was employed to examine associations of ERG parameters with the severity of DPN categorized by Baba's classification. Diagnostic properties of the device in DPN were evaluated using a receiver operating characteristic (ROC) curve.

RESULTS: Multiple regression model to predict the severity of DPN was generated using ERG. In the model, moderate to severe DPN was effectively diagnosed (area under the ROC curve 0.692, sensitivity 56.5%, specificity 78.3%, positive predictive value 70.6%, negative predictive value 66.1%, positive likelihood ratio 2.60, negative likelihood ratio 0.56). In the patients without DR, the implicit time and amplitude in ERG significantly correlated with parameters of NCS, baPWV, and IMT.

CONCLUSIONS: ERG parameters obtained by the hand-held device successfully predict the severity of DPN. The device might be useful to evaluate DPN.

Ichio, A. et al. Effects of Intravitreal Aflibercept on Retinal Function and Improvement of Macular Edema Associated With Diabetic Retinopathy, 2020

PURPOSE: To determine the effectiveness of intravitreal aflibercept (IVA) on the retinal function in eyes with diabetic macular edema (DME).

METHODS: Twenty-five eyes of 25 patients with DME were treated with three consecutive monthly IVA injections. The retinal sensitivities (RS) within the central 10° were determined by microperimetry (MP). The central subfield macular thickness (CMT) was determined by optical coherence tomography, and the implicit times (IT) and amplitudes (Amp) of the flicker electroretinograms (ERGs) were determined from the ERGs elicited and recorded by the RETeval. The number of microaneurysms (Mas) was counted in the fundus photographs. The assessments were made before the IVA injections (pre-IVA) and one week after the IVA injections (post-IVA). The correlations between the reduction ratio of the MA numbers/CMT and RS/IT/Amp were evaluated.

RESULTS: The mean RS improved from 19.9 ± 5.9 dB to 22.0 ± 5.8dB, the CMT decreased from 485.7 ± 90.6 μm to 376.9± 81.6 μm, and the number of Mas decreased from 49.6 ± 33.2 to 24.8 ± 18.1 after the IVA injection (all $P < 0.01$). The changes in the IT from 31.3 ± 3.3 ms to 31.5 ± 3.1 ms and the Amp from 12.2 ± 5.5 μV to 11.3 ± 6.1μV post-IVA were not significant. A significant correlation was found between the relative changes in the CMT and RS ($r=-0.43$; $P = 0.02$), the Mas and RS ($r=-0.38$; $P = 0.03$). No significant correlation was observed between the relative changes of the number of Mas/CMT and IT/Amp.

CONCLUSIONS: IVA can improve both central retinal function and anatomical conformation.

Motz C.T. et al. Novel detection and restorative levodopa treatment for pre-clinical diabetic retinopathy, 2020

PURPOSE: In this study, we proposed two goals: (1) to determine if a hand-held ERG device with a skin recording electrode had the sensitivity to measure OP delays in response to dim flash stimuli in persons with diabetes, without clinically detectable retinopathy and (2) to evaluate whether levodopa treatments could restore OP implicit time delays in persons with diabetes, without clinically detectable retinopathy.

METHOD: We recruited 15 control participants (male, n=12; female, n=3) between the ages of 37-69 years that had not been diagnosed with diabetes and without any confounding ocular diseases (i.e. retinitis, glaucoma, vitreous degeneration, high myopia, etc.) as verified by an eye exam within the last 6 months. To avoid difficulties when recording ERGs without dilation, patients with cataracts documented greater than 1+ nuclear sclerosis were also not included. We recruited participants with diabetes between the ages of 29-71 years (n=44, all male, Table 1) that had been identified as not having signs of retinopathy based on diabetic teleretinal screening fundus photographs from the Atlanta VA Eye Clinic in the last six months. Persons with diabetes were not included if they had any dopamine dysregulating diseases such as restless leg syndrome, Parkinson's disease, or major depressive disorder. Additionally, to avoid confounding effects as well as prevent drug interactions once treated with Sinemet, participants were excluded if they were on any dopamine enhancing drugs, such as DA agonists (i.e. bromocriptine, ropinirole, etc.) or monoamine oxidase inhibitors.

Participants were tested at baseline, two days (DM group only), two weeks, and four weeks. Testing consisted of ERG recordings, uncorrected visual acuity testing, and drifting spatial contrast sensitivity thresholds. Fundus photographs of eyes from the diabetic group included in the study were over-read by a comprehensive ophthalmologist (AYM), masked to the treatment groups, and confirmed that no signs of retinopathy were present.

RESULTS/ CONCLUSION: Our results show that early retinal dysfunction in persons with diabetes is detectable prior to clinically-recognized vascular changes using a hand-held ERG device with a novel dim stimulus, a skin electrode, and no dilating drops. These data indicate that recording dim flash OP delays could be used as a screening method to detect pre-clinical diabetic retinal dysfunction. Although contrast sensitivity as well as visual acuity deficits have been shown to be decreased in diabetic rodent models as well as humans, we did not observe any changes in our study for either test. (…). The lack of visual acuity and contrast sensitivity deficits in this study may be due to the fact that the study population had no clinically detectable DR, and visual acuity changes are often not seen until after clinical DR onset

In summary, these results show that early retinal dysfunction is detectable in the diabetic retina prior to clinically recognized retinopathy using a hand-held ERG system with skin electrodes. This ERG testing approach could be used to screen persons with diabetes in primary care clinics and other non-specialty eye clinics. These findings also show that early retinal dysfunction is reversible using levodopa treatments, suggesting reduced dopamine levels underlie early retinal function deficits. The recovery of dim OP delays within two weeks of treatment demonstrate that OP delays may be sensitive to early stage retinal dysfunction and provide a means to monitor both systemic and retinal-specific treatments for DM.

Chesler,K. Initiation of L-DOPA Treatment After Detection of Diabetes-Induced Retinal Dysfunction Reverses Retinopathy and Provides Neuroprotection in Rats, 2021

PURPOSE: L-DOPA treatment initiated at the start of hyperglycemia preserves retinal and visual function in diabetic rats. Here, we investigated a more clinically relevant treatment strategy in which retinal and visual dysfunction designated the beginning of the therapeutic window for L-DOPA treatment.

METHODS: Spatial frequency thresholds using optomotor response and oscillatory potential (OP) delays using electroretinograms were compared at baseline, 3, 6, and 10 weeks after streptozotocin (STZ) between diabetic and control rats. L-DOPA/carbidopa treatment (DOPA) or vehicle was delivered orally 5 days per week beginning at 3 weeks after STZ, when significant retinal and visual deficits were measured. At 10 weeks after STZ, retinas were collected to measure L-DOPA, dopamine, and 3,4-dihydroxyphenylacetic acid (DOPAC) levels using high-performance liquid chromatography.

RESULTS: Spatial frequency thresholds decreased at 6 weeks in diabetic vehicle rats (28%), whereas diabetic DOPA rats had stable thresholds (<1%) that maintained to 10 weeks, creating significantly higher thresholds compared with diabetic vehicle rats ($P < 0.0001$). OP2 implicit times in response to dim, rod-driven stimuli were decreased in diabetic compared with control rats (3 weeks, $P < 0.0001$; 10 weeks, $P < 0.01$). With L-DOPA treatment, OP2 implicit times recovered in diabetic rats to be indistinguishable from control rats by 10 weeks after STZ. Rats treated with L-DOPA showed significantly increased retinal L-DOPA ($P < 0.001$) and dopamine levels ($P < 0.05$).

CONCLUSIONS: L-DOPA treatment started after the detection of retinal and visual dysfunction showed protective effects in diabetic rats.

Swan, B. Evaluating Diabetic Retinopathy Screening Interventions in a Microsimulation Model, 2021

Diabetic retinopathy (DR) is the leading cause of blindness for working age Americans. Early detection, timely treatment, and appropriate follow-up care reduce the risk of severe vision loss from DR by 95%, yet, less than 50% of people with diabetes adhere to the recommended screening guidelines. Diabetes is a complicated disease for patients and their physicians to manage. We developed a microsimulation integrating the natural history model of DR with a patient's interaction with the care system. We introduced a DR screening device in primary care, with and without care coordination by a medical professional, in two interventions to the current care path. We found the interventions increased adherence of patients with vision-threatening DR (VTDR) to follow-up eye care, decreased the number of 'unnecessary' visits in specialty eye care from patients without VTDR, and decreased the total years spent blind.

Deng, X. A Diagnostic Model for Screening Diabetic Retinopathy Using the Hand-Held Electroretinogram Device RETeval, 2021

PURPOSE: To construct a proper model to screen for diabetic retinopathy (DR) with the RETeval.

METHOD: This was a cross-sectional study. Two hundred thirty-two diabetic patients and seventy controls were recruited. The DR risk assessment protocol was performed to obtain subjects' DR risk score using the RETeval. Afterwards, the receiver operating characteristic (ROC) curve was used to determine the best cutoff for diagnosing DR. Random forest and decision tree models were constructed.

RESULTS: With increasing DR severity, the DR score gradually increased. When the DR score was used to diagnose DR, the ROC curve had an area under the curve of 0.881 (95% confidence interval: 0.836-0.927, $P < 0.001$), with a best cutoff value of 22.95, a sensitivity of 74.3% (95 CI: 66.0%~82.6%), and a specificity of 90.6%(95 CI: 83.7% ~94.8%). The top four risk factors selected by the random forest were used to construct the decision tree for diagnosing DR, which had a sensitivity of 93.3% (95% CI: 86.3%~97.0%) and a specificity of 80.3% (95% CI: 72.1% ~86.6%).

CONCLUSIONS: The DR risk assessment protocol combined with the decision tree model was innovatively used to evaluate the risk of DR, improving the sensitivity of diagnosis, which makes this method more suitable than the current protocol for DR screening.

McAnany, J. Clinical electroretinography in diabetic retinopathy: A review, 2021

The electroretinogram (ERG) is a noninvasive, objective technique to evaluate retinal function that has become increasingly important in the study of diabetic retinopathy (DR).

We summarize the principles and rationale of the ERG, present findings from recent clinical studies that have used the full-field ERG, multifocal ERG, and pattern ERG to evaluate neural dysfunction in patients with diabetes, and weigh the strengths and limitations of the technique as it applies to clinical studies and management of patients with diabetic retinopathy. Taken together, ERG studies have provided convincing evidence for dysfunction of the neural retina in patients with diabetes, including those who have no clinically-apparent retinal vascular abnormalities. Recent full-field ERG findings have pointed to the intriguing possibility that photoreceptor function is abnormal in early-stage disease. Pattern ERG data, in conjunction with recently developed photopic negative response analyses, indicate inner retina dysfunction. In addition, multifocal ERG studies have shown spatially localized neural abnormalities that can predict the location of future microaneurysms. Given the insights provided by the ERG, it is

likely to play a growing role in understanding the natural history of neural dysfunction in diabetes, as well as providing an attractive outcome measure for future clinical trials that target neural preservation in DR.

Simó, R. Neurovascular Unit: A New Target for Treating Early Stages of Diabetic Retinopathy, 2021

The concept of diabetic retinopathy as a microvascular disease has evolved and is now considered a more complex diabetic complication in which neurovascular unit impairment plays an essential role and, therefore, can be considered as a main therapeutic target in the early stages of the disease. However, neurodegeneration is not always the apparent primary event in the natural story of diabetic retinopathy, and a phenotyping characterization is recommendable to identify those patients in whom neuroprotective treatment might be of benefit. In recent years, a myriad of treatments based on neuroprotection have been tested in experimental models, but more interestingly, there are drugs with a dual activity (neuroprotective and vasculotropic). In this review, the recent evidence concerning the therapeutic approaches targeting neurovascular unit impairment will be presented, along with a critical review of the scientific gaps and problems which remain to be overcome before our knowledge can be transferred to clinical practice.

Zhuang, X. Multimodal imaging analysis for the impact of retinal peripheral lesions on central neurovascular structure and retinal function in type 2 diabetes with diabetic retinopathy, 2022

OBJECTIVES: To explore the possible role of peripheral lesions (PLs) detected by ultrawide field (UWF) imaging system on central neurovascular structure and retinal function.

METHODS: Ninety-seven diabetic patients were included in this cross-sectional study using UWF pseudocolour colour imaging with Optos Daytona (Optos, PLC). UWF images were graded as with predominantly peripheral lesions (PPLs) and without PPL. Macular neurovascular alterations and retinal function were measured by optical coherence tomography angiography (OCTA) and RETeval device, respectively. Central microcirculation and retinal function were compared between eyes with and without PPL.

RESULTS: The study evaluated 186 eyes (97 patients; 43 females (44.3%)), including 92 eyes without PPL and 94 eyes with PPL. Central retinal vessel density was comparable between eyes with and without PPL. Delayed implicit time and decreased pupil area ratio were found in the PPL group compared with eyes without PPL, and this difference remained unchanged after adjusting for systemic factors (all $p < 0.01$).

CONCLUSIONS: Our study suggests that retinal function is worse in diabetic eyes with PPL. These findings challenged the conventional ETDRS protocols which ignored peripheral retina in determining DR severity. Furthermore, combining UWF imaging with RETeval system to detect more retinal abnormalities may be helpful in DR management.

Muto, T. Intravitreal Fasudil for Treatment of Diabetic Macular Edema with an Unfavorable Response, 2022

PURPOSE: This study evaluates the effect of intravitreal injection of a Rho-associated protein kinase (ROCK) inhibitor, fasudil, on diabetic macular edema (DME) with an unfavorable response.

METHODS: This study included 14 eyes of 13 patients (mean age: 65.7 ± 5.2 years) with DME, and eligible eyes underwent single intravitreal injection of 0.025 mg fasudil. The best-corrected visual acuity (BCVA), intraocular pressure (IOP), and central macular thickness (CMT) were evaluated before and 1, 2, and 3 months after treatment. The standard automated perimetry (SAP) results and maximal response of the electroretinogram (ERG) were recorded before and 3 months after treatment.

RESULTS: The BCVA, IOP, and CMT remained unchanged during the study period. Similarly, the mean deviation obtained by SAP and each ERG parameter did not show significant changes after the treatment.

CONCLUSIONS: Although single intravitreal fasudil injection failed to show therapeutic benefits in DME, it seemed to have no negative effect on the retina.

Jia, Y. Are we overlooking the neurodegeneration in the early stage of Type 1 Diabetes Mellitus without Visual Impairment or Diabetic Retinopathy: is it probably occurred before retinal vasculature dysfunction?, 2022

PURPOSE. Using electrophysiology (ERG) to investigate the early alterations of retinal function in diabetic children and adolescents without diabetic retinopathy (DR) or visual impairment (VI).

METHODS. We recorded and compared the data of full-field flicker ERGs between 59 normal subjects and 60 children and adolescents with type 1 diabetes mellitus (T1DM) from the Children's Hospital of Fudan University in Shanghai.

RESULTS. In both groups, patients with diabetes and healthy controls were matched for age, gender, weight, height, BMI, intraocular pressure (IOP), and best-corrected visual acuity (BCVA). Among the parameters of the outcomes of ERG, the implicit time in eyes in DM patients was significantly prolonged compared to normal eyes (P=0.008, 16 Td-s; P=0.000, 32 Td-s). In the case group, we found significantly positive correlation between implicit time and BMI (P<0.05), as well as implicit time and axial length (AL).

CONCLUSIONS. The study reveals that the dysfunction of retina in DM children can be detected with ERGs. It also shows that hyperglycaemia has an impact on the occurrence of neurodegeneration in the early stage of DM.

Kirthi, V. Multimodal testing reveals subclinical neurovascular dysfunction in prediabetes, challenging the diagnostic threshold of diabetes, 2023

AIM: To explore if novel non-invasive diagnostic technologies identify early small nerve fibre and retinal neurovascular pathology in prediabetes.

METHODS: Participants with normoglycaemia, prediabetes or type 2 diabetes underwent an exploratory cross-sectional analysis with optical coherence tomography angiography (OCT-A), handheld electroretinography (ERG), corneal confocal microscopy (CCM) and evaluation of electrochemical skin conductance (ESC).

RESULTS: Seventy-five participants with normoglycaemia (n = 20), prediabetes (n = 29) and type 2 diabetes (n = 26) were studied. Compared with normoglycaemia, mean peak ERG amplitudes of retinal responses at low (16-Td·s: 4.05 μV, 95% confidence interval [95% CI] 0.96–7.13) and high (32-Td·s: 5·20 μV, 95% CI 1.54–8.86) retinal illuminance were lower in prediabetes, as were OCT-A parafoveal vessel densities in superficial (0.051 pixels/mm2, 95% CI 0.005–0.095) and deep (0.048 pixels/mm2, 95% CI 0.003–0.093) retinal layers. There were no differences in CCM or ESC measurements between these two groups. Correlations between HbA1c and peak ERG amplitude at 32-Td·s ($r = -0.256$, $p = 0.028$), implicit time at 32-Td·s ($r = 0.422$, $p < 0.001$) and 16-Td·s ($r = 0.327$, $p = 0.005$), OCT parafoveal vessel density in the superficial ($r = -0.238$, $p = 0.049$) and deep ($r = -0.3$, $p = 0.017$) retinal layers, corneal nerve fibre length (CNFL) ($r = -0.293$, $p = 0.017$), and ESC-hands ($r = -0.244$, $p = 0.035$) were observed. HOMA-IR was a predictor of CNFD ($\beta = -0.94$, 95% CI −1.66 to −0.21, $p = 0.012$) and CNBD ($\beta = -5.02$, 95% CI −10.01 to −0.05, $p = 0.048$).

CONCLUSIONS: The glucose threshold for the diagnosis of diabetes is based on emergent retinopathy on fundus examination. We show that both abnormal retinal neurovascular structure (OCT-A) and function (ERG) may precede retinopathy in prediabetes, which require confirmation in larger, adequately powered studies.

Weerasinghe, L. Diabetic Retinopathy Screening at the Point of Care (DR SPOC): detecting undiagnosed and vision-threatening retinopathy by integrating portable technologies within existing services, 2023

INTRODUCTION: The aim of this study was to determine the prevalence of diabetic retinopathy (DR) in a low socioeconomic region of a high-income country, as well as determine the diagnostic utility of point-of-care screening for high-risk populations in tertiary care settings.

RESEARCH DESIGN AND METHODS: This was a cross-sectional study of patients with diabetes attending foot ulcer or integrated care diabetes clinics at two Western Sydney hospitals (n=273). DR was assessed using portable, two-field, non-mydriatic fundus photography and combined electroretinogram/ pupillometry (ERG). With mydriatic photographs used as the reference standard, sensitivity and specificity of the devices were determined. Prevalence of DR and vision-threatening diabetic retinopathy (VTDR) were reported, with multivariate logistic regression used to identify predictors of DR.

RESULTS: Among 273 patients, 39.6% had any DR, while 15.8% had VTDR, of whom 59.3% and 62.8% were previously undiagnosed, respectively. Non-mydriatic photography demonstrated 20.2% sensitivity and 99.5% specificity for any DR, with a 56.7% screening failure rate. Meanwhile, mydriatic photography produced high-quality images with a 7.6% failure rate. ERG demonstrated 72.5% sensitivity and 70.1% specificity, with a 15.0% failure rate. The RETeval ERG was noted to have an optimal DR cut-off score at 22. Multivariate logistic regression identified an eGFR of ≤29 mL/min/1.73 m2, HbA1c of ≥7.0%, pupil size of <4 mm diameter, diabetes duration of 5–24 years and RETeval score of ≥22 as strong predictors of DR.

CONCLUSION: There is a high prevalence of vision threatening and undiagnosed DR among patients attending high-risk tertiary clinics in Western Sydney. Point-of-care DR screening using portable, mydriatic photography demonstrates potential as a model of care which is easily accessible, targeted for high-risk populations and substantially enhances DR detection.

Dou, N. Association between choroidopathy and photoreceptors during the early stage of diabetic retinopathy: a cross-sectional study, 2023

PURPOSE: To explore the role of choroidopathy in diabetic retinopathy (DR) by investigating the correlation between alterations of choroidal vessel and photoreceptors during the early stage of DR.

METHODS: We performed a cross-sectional comparison of diabetic patients without DR (NDR group; n=16) and those with mild nonproliferative diabetic retinopathy (NPDR group; n=39). Optical coherence tomography (OCT) images of choroidal vessel alterations and photoreceptor structures were evaluated using the choroidal vascularity index (CVI) and adjusted ellipsoid zone (EZ) reflectivity, respectively. To evaluate the function of cone photoreceptors, the fundamental, harmonic amplitudes, the parameters S and Rmp3 were calculated from the electroretinogram (ERG). These factors were compared between groups. The correlation between the CVI and parameters describing the function and structure of the photoreceptors was evaluated.

RESULTS: The significant decrease was observed in the CVI in the NPDR group compared to the NDR group (0.67 ± 0.04 vs. 0.70 ± 0.06; p = 0.028), but not in the adjusted EZ reflectivity or ERG parameters. In NPDR group and merging the 2 groups, CVI was moderately positively correlated with the fundamental amplitude obtained by the flicker ERG (NPDR only: r = 0.506; p = 0.001; merge the 2 groups: r = 0.423; p = 0.001), which was regulated by the response of the cone photoreceptors. The CVI was positively and moderately correlated with the logS (NPDR only: r = 0.462; p = 0.003; merge the 2 groups: r = 0.355; p = 0.008), indicating the sensitivity of cone cell light transduction.

CONCLUSION: Compared to eyes without DR, CVI decreased representing choroidal vascular changes in eyes with mild NPDR. These changes may be related to the functional impairment of cone photoreceptors, especially phototransduction sensitivity, as the DR develops.

Deng, X. The association between decreased choriocapillary flow and electroretinogram impairments in patients with diabetes, 2023

PURPOSE: To evaluate the association between choriocapillary flow (CCF) and electroretinogram (ERG) in patients with diabetes.

METHOD: This was a cross-sectional study. Patients with type 2 diabetes and healthy controls who had undergone both flicker ERG and optical coherence tomography angiography (OCTA) were included, while patients with severe diabetic retinopathy (DR) and macular edema were excluded. Correlations among OCTA and ERG pa rameters were conducted by generalized linear mixed models (GLMM).

RESULT: One hundred ninety-four eyes of 102 patients with diabetes and fifty-six eyes of 28 controlswere included. The implicit time of 30-Hz flicker ERG successively increased, while the amplitudes, inner-retina vessel density and CCF were decreased from the control to the nondiabetic retinopathy (NDR) to DR group. In patients with diabetes, all GLMM models of ERG parameters had statistically significance (P<0.05), and CCF was correlated with ERG parameters (coefficient index=-0.601, P< 0.001 with 16 Td-s implicit time; coefficient index=-0.687, P< 0.001 with 32 Td-s implicit time; coefficient index=0.933, P=0.035 with 32 Td-s amplitude) and the thickness of retinal pigment epithelium, while in the GLMM model of CCF, it was correlated with the thickness of retinal pigment epithelium and the level of glycosylated hemoglobin(both P= 0.001).

CONCLUSION: CCF decreased in patients with diabetes, and it was related with ERG. Choroidopathy and its functional impairment in the retina may occur very early in patients with diabetes by influencing the outer retina.

Simó, R. What else can we do to prevent diabetic retinopathy?, 2023

The classical modifiable factors associated with the onset and progression of diabetic retinopathy are the suboptimal control of blood glucose levels and hypertension, as well as dyslipidaemia. However, there are other less recognised modifiable factors that can play a relevant role, such as the presence of obesity or the abnormal distribution of adipose tissue, and others related to lifestyle such as the type of diet, vitamin intake, exercise, smoking and sunlight exposure. In this article we revisit the prevention of diabetic retinopathy based on modulating the modifiable risk factors, as well as commenting on the potential impact of glucose-lowering drugs on the condition. The emerging concept that neurodegeneration is an early event in the development of diabetic retinopathy points to neuroprotection as a potential therapeutic strategy to prevent the advanced stages of the disease. In this regard, the better phenotyping of very early stages of diabetic retinopathy and the opportunity of arresting its progression using treatments targeting the neurovascular unit (NVU) are discussed.

Arias-Alvarez, M. Electrophysiological findings in long-term type 1 diabetes patients without diabetic retinopathy using different ERG recording systems, 2024

To assess full-field electroretinogram findings in long-term type 1 diabetes patients without diabetic retinopathy. Prospective study including 46 eyes of 23 patients with type 1 diabetes and 46 agematched healthy eyes evaluated by the RETI-port/scan21 and the portable system RETeval following ISCEV guidelines. The average duration of diabetes was 28.88 ± 8.04 years. In scotopic conditions, using the RETI-port/scan21, diabetic patients showed an increase in b-wave implicit time (IT) (p = 0.017) with the lowest stimuli; a diminished b-wave amplitude (p= 0.005) in the mixed response, an increased IT (p = 0.004) with the high-intensity stimuli and an OP2 increased IT (p= 0.008) and decreased amplitude (p = 0.002). Under photopic conditions, b-wave amplitude was lower (p< 0.001) and 30-Hz flicker response was diminished (p = 0.021). Using the RETeval, in scotopic conditions, diabetic patients showed a reduction in the rod b-wave amplitude (p = 0.009), an increase in a-wave IT with the 280 Td.s stimulus (p = 0.005). OP2 had an increased IT and diminished amplitude (p= 0.003 and p = 0.002 respectively). 16 Td.s flicker showed an increased IT (p= 0.008) and diminished amplitude (p = 0.048). Despite variations in values between both systems, nearly all results displayed positive correlations. Long-term type 1 diabetes patients without diabetic retinopathy exhibit alterations in scotopic conditions, as evidenced by both conventional and portable electroretinogram devices. These findings suggest a modified retinal function, particularly in rod-driven pathways, even in the absence of vascular signs.

Glassmann, M. Electrophysiological findings in long-term type 1 diabetes patients without diabetic retinopathy using different ERG recording systems, 2024

TOPIC: Visual function impairment from diabetic retinopathy can have a considerable impact on patient's quality of life. Best-corrected visual acuity (BCVA) is most commonly used to assess visual function and guide clinical trials. However, BCVA is affected late in the disease process, is not affected in early disease, and does not capture some of the visual disturbances described by patients with diabetes.

CLINICAL RELEVANCE: The goal of this report is to evaluate the relationship between diabetic retinal disease (DRD) and visual function parameters to determine which if any of them may be used in a future DRD staging system.

METHODS: The visual functions working group was one of 6 areas of DRD studied as part of the DRD Staging System update, a project of the Mary Tyler Moore Vision Initiative (MTM Vision). The working group identified 12 variables of possible interest, seven of which were judged to have sufficient preliminary data to suggest an association with DR to warrant further review; microperimetry, static automated perimetry (SAP), ERG oscillatory potentials, flicker ERG, low luminance VA (LLVA), contrast sensitivity (CSF) and best-corrected visual acuity (BCVA). The objective field analyzer (OFA) was added after subsequent in-person workshops.

RESULTS: Currently, the only visual function test available for immediate use is BCVA; the remaining tests are either promising (within 5 years) or have potential (>5 years) use. Besides BCVA, most visual function tests had a limited role in current clinical care, however LLVA, CSF, Flicker ERG and OFA demonstrated potential for screening and research purposes.

CONCLUSION: Although current visual function tests are promising, future prospective studies involving patients with early and more advanced retinopathy are necessary to determine if these tests can be used clinically or as endpoints for clinical studies.

Imm, N. Preventable risk factors for type 2 diabetes can be detected using noninvasive spontaneous electroretinogram signals, 2024

Given the ever-increasing prevalence of type 2diabetes and obesity, the pressure on global healthcare is expected to be colossal, especially in terms of blindness. Electroretinogram (ERG) has long been perceived as a first-use technique for diagnosing eye diseases, and some studies suggested its use for preventable risk factors of type 2 diabetes and thereby diabetic retinopathy (DR). Here, we show that in non-evoked mode, ERG signals contain spontaneous oscillations that predict disease cases in rodent models of obesity and in people with overweight, obesity, and metabolic syndrome but not yet diabetes, using one single random forest-based model. Classification performance was both internally and externally validated, and correlation analysis showed that the spontaneous oscillations of the non evoked ERG are altered before oscillatory potentials, which are the current gold-standard for early DR. Principal component and discriminant analysis suggested that the slow frequency (0.4–0.7 Hz) components are the main discriminators for our predictive model. In addition, we established that the optimal conditions to record these informative signals, are 5-minute duration recordings under daylight conditions, using any ERG sensors, including ones working with portative, non-mydriatic devices. Our study provides an early warning system with promising applications for prevention, monitoring and even the development of new therapies against type 2 diabetes.

Hughes-Cano, JA. Improved predictive diagnosis of diabetic macular edema based on hybrid models: An observational study, 2024

Diabetic Macular Edema (DME) is the most common sight-threatening complication of type 2 diabetes. Optical Coherence Tomography (OCT) is the most useful imaging technique to diagnose, follow up, and evaluate treatments for DME. However, OCT exam and devices are expensive and unavailable in all clinics in low- and middle-income countries. Our primary goal was therefore to develop an alternative method to OCT for DME diagnosis by introducing spectral information derived from spontaneous electroretinogram (ERG) signals as a single input or combined with fundus that is much more widespread. Baseline ERGs were recorded in 233 patients and transformed into scalograms and spectrograms via Wavelet and Fourier transforms, respectively. Using transfer learning, distinct Convolutional Neural Networks (CNN) were trained as classifiers for DME using OCT, scalogram, spectrogram, and eye fundus images. Input data were randomly split into training and test sets with a proportion of 80 % –20 %, respectively. The top performers for each input type were selected, OpticNet-71 for OCT, DenseNet-201 for eye fundus, and non-evoked ERG-derived scalograms, to generate a combined model by assigning different weights for each of the selected models. Model validation was performed using a dataset alien to the training phase of the models. None of the models powered by mock ERG-derived input performed well. In contrast, hybrid models showed better results, in particular, the model powered by eye fundus combined with mock ERG-derived information with a 91 % AUC and 86 % F1-score, and the model powered by OCT and mock ERG-derived scalogram images with a 93 % AUC and 89 % F1-score. These data show that the spontaneous ERG derived input adds predictive value to the fundus- and OCT-based models to diagnose DME, except for the sensitivity of the OCT model which remains the same. The inclusion of mock ERG signals, which have recently been shown to take only 5 min to record in daylight conditions, therefore represents a potential improvement over existing OCT-based models, as well as a reliable and cost-effective alternative when combined with the fundus, especially in underserved areas, to predict DME.

Kirika, K. Electroretinograms Recorded with Skin Electrodes from Post-Vitrectomy Silicone Oil Filled Eyes with Proliferative Diabetic Retinopathy, 2024

PURPOSE: To determine the physiological status of the retina by electroretinography (ERG) using skin electrodes and the RETevalTM system in eyes that had undergone pars plana vitrectomy (PPV) with silicone oil (SO) tamponade. The vitrectomy was performed for a retinal detachment and proliferative diabetic retinopathy (PDR).
DESIGN: Retrospective case series.
METHODS: ERGs were recorded with the RETevalTM system (LKC Technologies Inc. Gaithersburg, MD; Welch Allyn, Inc. Skaneateles Falls, NY) from eight eyes with PDR before and after the SO removal. The amplitudes and implicit times of the a- and b-waves of the ERGs before the SO removal were compared to that after the SO removal.
RESULTS: ERGs were recordable in four eyes before and after the SO removal and the a- and b-amplitudes improved in three eyes and worsened in one eye after the SO removal. In the remaining four eyes, ERGs were non-recordable both before and after the SO removal.
CONCLUSION: These results indicate that ERGs picked up by skin electrodes can be used to assess the physiology of the retina in eyes with a SO tamponade. The flat ERGs in the SO-filled eye indicated the presence of diffuse retinal damage which was confirmed by the flat ERGs after the SO removal.
PLAIN LANGUAGE SUMMARY: There has been an increasing number of reports on evaluating the retinal function using electroretinography (ERG) with skin electrodes. The main advantage of this system is the ability to record ERGs with a skin electrode that does not touch the cornea and ocular surface. This reduces the risk of infection especially in the postoperative period and in clinical situations where infection is suspected. In addition, there have been only a few reports evaluating the function of the retina by ERG in SO-filled eyes. We recorded ERGs with the RETeval (LKC Technologies Inc. Gaithersburg, MD; Welch Allyn Inc. Skaneateles Falls, NY) device, a relatively new ERG recording system that uses skin electrodes and is less invasive. We recorded ERGs from eight SO-filled eyes with proliferative diabetic retinopathy (PDR). In 4 SO filled eyes, the amplitudes increased in three eyes after the SO removal. In the other four eyes, ERGs were non-recordable before and after the SO removal. These results suggest that the RETeval system that uses skin electrodes can be used to assess the retinal function in PDR eyes with a SO tamponade. We suggest that the absence of ERGs in the SO filled eyes was not due to the electrical non-conductive effects of SO but may indicate the presence of diffuse retinal damage which was confirmed after the SO removal.

Micheletti, M. Current and Next Generation Portable Screening Devices for Diabetic Retinopathy, 2024

Diabetic retinopathy (DR) is the leading cause of legal blindness in the United States, and with the growing epidemic of diabetes, a global increase in the incidence of DR is inevitable, so it is of utmost importance to identify the most costeffective tools for DR screening. Emerging technology may provide advancements to offset the burden of care, simplify the process, and provide financially responsible methods to safely and effectively optimize care for patients with diabetes mellitus (DM). We review here currently available technology, both in production and under development, for DR screening. Preliminary results of smartphone-based devices, “all-in-one” devices, and

alternative technologies are encouraging, but are largely pending verification of utility when used by nonophthalmic personnel. Further research comparing these devices to current nonportable telemedicine strategies and clinical fundus examination is necessary to validate these techniques and to potentially overcome the poor compliance around the globe of current strategies for DR screening.

Pearce, E. A Review of Advancements and Evidence Gaps in Diabetic Retinopathy Screening Models, 2024

Diabetic retinopathy (DR) is a microvascular complication of diabetes with a prevalence of ~35%, and is one of the leading causes of visual impairment in people of working age in most developed countries. The earliest stage of DR, non-proliferative DR (NPDR), may progress to sight-threatening DR (STDR). Thus, early detection of DR and active regular screening of patients with diabetes are necessary for earlier intervention to prevent sight loss. While some countries offer systematic DR screening, most nations are reliant on opportunistic screening or do not offer any screening owing to limited healthcare resources and infrastructure. Currently, retinal imaging approaches for DR screening include those with and without mydriasis, imaging in single or multiple fields, and the use of conventional or ultra-wide-field imaging. Advances in telescreening and automated detection facilitate screening in previously hard-to-reach communities. Despite the heterogeneity in approaches to fit local needs, an evidence base must be created for each model to inform practice. In this review, we appraise different aspects of DR screening, including technological advances, identify evidence gaps, and propose several studies to improve DR screening globally, with a view to identifying patients with moderate-to-severe NPDR who would benefit if a convenient treatment option to delay progression to STDR became available.

Rai, C. Early diabetic eye damage: Comparing detection methods using diagnostic power, 2024

It is now clear that retinal neuropathy precedes classical microvascular retinopathy in diabetes. Therefore, tests that underpin useful new endpoints must provide high diag nostic power well before the onset of moderate diabetic retinopathy. Hence, we compare detection methods of early diabetic eye damage. We reviewed data from a range of functional and structural studies of early diabetic eye disease and computed standardized effect size as a measure of diagnostic power, allowing the studies to be compared quantitatively. We then derived minimum performance criteria for tests to provide useful clinical endpoints. This included the criteria that tests should be rapid and easy so that children with type 1 diabetes can be followed into adulthood with the same tests. We also defined attributes that lend test data to further improve performance using Machine/Deep Learning. Data from a new form of objective perimetry suggested that the criteria are achievable.

McAnany, J. Brief report: harmonic analysis of the 30 Hz flicker ERG in early-stage diabetic retinopathy, 2025

PURPOSE: To determine if harmonic components of the 30 Hz flicker ERG are useful for detecting neural dysfunction in diabetics who have mild or no nonproliferative diabetic retinopathy (NPDR).
METHODS: Previously reported light-adapted flicker ERG data recorded from 20 diabetics who had no clinically-apparent retinopathy (NDR), 20 who had mild NPDR (MDR), and 20 non-diabetic controls were reanalyzed. From this dataset, the amplitude and phase of the 31.25 Hz flicker ERG fundamental and second harmonic were extracted. The 62.5 Hz flicker ERG fundamental was also extracted. Similar responses were also acquired prospectively from 10 controls, 5 NDR, and 5 MDR subjects, comprising a second dataset.
RESULTS: Analysis of variance indicated that both diabetic groups had normal amplitudes elicited by the 31.25 Hz stimulus (fundamental and second harmonic), whereas the 62.5 Hz amplitude was reduced significantly in both diabetic groups. This pattern was found in both the retrospective and prospective analyses.
CONCLUSION: The second harmonic of the 31.25 Hz flicker response (equivalent to 62.5 Hz) was normal in early-stage DR, whereas the response to 62.5 Hz flicker stimuli was abnormal. The second harmonic of the ISCEV standard 30 Hz flicker ERG does not appear to be a useful indicator of neural dysfunction in early DR.

Davis, Q. Predicting Progression to Vision-Threatening Complications in Diabetic Retinopathy, 2025

OBJECTIVE: To characterize the performance of 56 parameters from electroretinography (ERG) / pupillometry, color fundus photography (FP), optical coherence tomography angiography (OCTA), and ultra-widefield fluorescein angiography (UWF-FA) for predicting which subjects with non-proliferative diabetic retinopathy (DR) will progress to vision-threating complications (VTC) within 48 weeks.
DESIGN: A longitudinal prospective study from 44 trial sites in the US.
PARTICIPANTS: Subjects had moderate to severe non-proliferative diabetic retinopathy (NPDR) and no center-involved diabetic macular edema. Among the 162 subjects, the mean age was 57 years and 58% were male.
INTERVENTION: Although this study tested an experimental drug, there was no indication of a treatment effect. Results are analyzed over all subjects regardless of study treatment.

MAIN OUTCOME MEASURES: Specialized reading centers measured 56 parameters from 4 testing modalities (ERG / pupillometry, FP, OCTA, and UWF-FA) to evaluate DR status. Kaplan-Meier analysis and a Cox proportional hazards model were applied to each parameter to identify significant predictors of progression to VTC, defined as progression to proliferative diabetic retinopathy, diabetic macular edema, or treatment thereof.
RESULTS: Of the 56 parameters, the strongest predictor of progression in the following 48 weeks was the RETeval DR Score, which combines ERG and pupil response. A DR score ≥26.9 had a relative risk (RR) of 5.6 ($p<0.0001$). The most-predictive parameter from the other modalities were UWF-FA's total ischemia index ≥ 0.125 with a RR of 5.3 ($p < 0.0001$), OCTA's foveal avascular zone area ≥ 0.295 mm2 with a RR of 3.6 ($p < 0.05$), and FP's diabetic retinopathy severity score (DRSS) ≥ 47 (moderate NPDR) with a RR of 2.1 ($p<0.05$).
CONCLUSION: Both functional (ERG, pupil response) and structural (FP, OCTA, UWF-FA) testing can predict progression to VTC from DR, with the DR Score having the best predictive capability. These results suggest it is possible to improve the DR staging system which in turn may enable better allocation of healthcare resources.

Fickweiler, W. Advancing Toward a World Without Vision Loss From Diabetes: Insights From The Mary Tyler Moore Vision Initiative Symposium 2024 on Curing Vision Loss From Diabetes, 2025

The Mary Tyler Moore Vision Initiative (MTM Vision) honors Mary Tyler Moore's commitment to ending vision loss from diabetes. Founded by Moore's husband, Dr. S. Robert Levine, MTM Vision aims to accelerate breakthroughs in diabetic retinal disease (DRD). At the MTM Vision Symposium 2024 on Curing Vision Loss from Diabetes, experts highlighted the urgent need for updated DRD staging systems, clinically relevant endpoints, and novel biomarkers to detect early disease changes. MTM Vision is advancing two clinical trials in collaboration with the DRCR Retina Network, launching a public awareness campaign, and welcoming Boehringer Ingelheim as the first founding industry member of its pre-competitive Consortium. Speakers emphasized big-data strategies and artificial intelligence (AI)-driven tools to improve DRD diagnosis, risk prediction, and personalized treatment. They also showcased new efforts to bridge academic discoveries with industry expertise, illustrating promising work on vascular regeneration and cellular senescence that may yield future therapies. The MTM Vision Biorepository and Resource Center is expanding tissue collections, enabling multi-omics analyses to study DRD mechanisms. Patient voices were central to the discussion, with calls for enhanced patient-reported outcomes, caregiver support, and broader education on DRD's risks. The symposium also underscored the importance of integrating mental health, quality of life measures, and ongoing patient input to guide clinical research.

Levine, S. Report of the 2023 Mary Tyler Moore Vision Initiative Workshop, 2025

The Mary Tyler Moore Vision Initiative (MTM Vision) Diabetic Retinal Disease (DRD) Clinical Endpoints Workshop was held on November 14, 2023. More than 130 clinicians, scientists, and representatives from funding and regulatory agencies, diagnostic, therapeutic, and biotech industry and patient advocates discussed the needs for new diagnostic and therapeutic approaches to preserve and restore retinal neurovascular unit integrity in people with diabetes. MTM Vision projects, notably updating the DRD staging system and severity scale, establishing a human ocular biorepository and resource, and validating useful clinical endpoints and biomarkers to accelerate development of new drugs and improve patient care were emphasized. A public-private consortium is essential to fulfill the objectives of MTM Vision for the benefit of persons with diabetes.

Gonmori, M. Comparisons of oscillatory potentials and 30 Hz flicker electroretinograms for discriminating eyes with diabetic retinopathy from normal eyes, 2025

PURPOSE: To compare the amplitudes and implicit times of the oscillatory (OPs) of the full-field electroretinograms (ERGs) to those of the 30 Hz flicker ERGs in differentiating eyes with diabetic retinopathy (DR) from normal eyes.

STUDY DESIGN: Single-center observational study.

METHODS: Full-field ERGs were recorded in 55 patients with Type 2 diabetes mellitus (DM) and 20 normal control subjects. The amplitudes and implicit times of the OPs and of the 30 Hz flicker ERGs were measured. Optical coherence tomography angiography (OCTA) was used to record 3×3 mm enface images of the retina from which the vascular density (VD) of the superficial capillary plexus (SCP) and deep capillary plexus (DCP) were obtained. The receiver operating characteristic (ROC) curves were used to determine the ability of each ERG parameter to discriminate diseased eyes from normal eyes. The significance of the correlations between each ERG parameter and the VD of the SCP and DCP was determined.

RESULTS: The area under the ROC curves (AUCs) was significantly larger for the implicit times than for the amplitudes of each ERG component ($P<0.005$). There were no significant differences in the AUCs between the OPs and 30 Hz flicker ERGs in differentiating eyes with DM or DR from normal eyes. The implicit time of the 30 Hz flicker ERG had the highest significant correlation coefficient with the VD of the DCP ($r = -0.31$, $P <0.001$).

CONCLUSIONS: The OPs and 30 Hz flicker ERGs have equal ability in differentiating eyes with DR from normal eyes but with better ability for the implicit times than the amplitudes. The implicit time of the 30 Hz flicker ERG is the most sensitive parameter that is correlated with the reduction of VD among the full-field ERG components.

Moore, F. Sustained Benefit of Short-Term Levodopa Treatment on Inner Retinal Function in Patients With Diabetes, 2025

PURPOSE: This study investigated the long-term progression of oscillatory potential (OP) implicit times (ITs) in individuals with preclinical diabetic retinopathy (DR) with and without levodopa (L-DOPA) treatment by quantifying functional and structural retinal changes.

METHODS: Participants from the Motz et al. (2020) study were re-evaluated after 5 years, including individuals with diabetes mellitus (DM) who received L-DOPA treatment for 2 weeks (the DM + L-DOPA group; n = 14), those who did not (the DM group; n = 6), and non-diabetic healthy controls (the control group; n = 37). Retinal function and structure were assessed using dim-flash electroretinography (ERG) and optical coherence tomography (OCT).

RESULTS: After 5 years, OP 1 and OP 2 ITs showed no significant differences among the groups ($P > 0.05$). The DM + L-DOPA OP IT values remained improved compared to baseline. The outer region thickness of the outer plexus layer (OPL) and ganglion cell layer (GCL) were significantly thinner in the DM + L-DOPA group compared to the DM group ($P < 0.05$). The DM group showed strong correlations between OP IT and OCT thickness across all retinal regions, whereas the DM + L-DOPA group correlations were similar to the control group.

CONCLUSIONS: Short-term L-DOPA treatment led to significant functional improvements after 2 weeks, with trends suggesting sustained benefit over 5 years. Inner retinal structural differences suggest potential long-term benefit of L-DOPA on retinal health. These findings support OP IT delays as early biomarkers for preclinical DR and suggest L-DOPA may provide lasting neuroprotective benefits.

TRANSLATIONAL RELEVANCE: Retinal dysfunction and inner retinal structural changes could be potential biomarkers for preclinical DR, and L-DOPA treatment may provide sustained benefits for the diabetic retina.

Sugiura-Roth, Y. The DR score in RETeval™ electroretinogram system facilitates expeditious and uncomplicated early detection and assessment of diabetic polyneuropathy in clinical practice, 2025

PURPOSE: The principal aim of this investigation was to assess the utility of a novel DR score for the early detection of diabetic polyneuropathy (DPN). This score, currently integrated into the RETevalTM electroretinogram (ERG) system, is derived from parameters such as ERG wave characteristics, patient age, and pupillary response. Traditional nerve conduction studies (NCS), though valuable, have notable limitations, including the necessity for costly equipment and specialized personnel. Consequently, it was postulated that the DR score—initially devised for predicting diabetic retinopathy—might serve as a practical alternative for diagnosing DPN. This study sought to test the hypothesis that the DR score could offer a reliable means of both diagnosing DPN and estimating its severity.

METHODS: The study retrospectively analyzed 82 diabetic patients admitted to Aichi Medical University Hospital between November 2016 and January 2019. ERG was performed using the RETevalTM device, and NCS was conducted to classify DPN stages according to the Baba's Differentiation Classification (BDC) system. Multiple regression analysis and receiver operating characteristics (ROC) analysis were employed to assess the relationship between the DR score and DPN stages.

RESULTS: Among 82 participants, 24.4% (n = 20) had no DPN (stage 0), and 75.6% (n = 62) had stage 1 or higher DPN. The DR score was significantly correlated with various clinical parameters, including nerve conduction velocities and the severity of DPN as classified by BDC stages. The regression model showed that both the DR score and age were significant predictors of DPN severity. The ROC analysis demonstrated that the DR score had a moderate ability to discriminate between no DPN and stage 1 or more of DPN, with an area under the ROC curve of 0.738.

CONCLUSIONS: In conclusion, this study involving 82 patients suggests that the DR score may be a valuable tool for the early detection and staging of DPN, potentially offering a more accessible and cost-effective alternative to traditional NCS, with significant implications for improving diabetic care.

Sirek, S. Use of the RETevalTM Handheld Electroretinogram Device for Assessing the Risk of Diabetic Retinopathy in Patients With Type 1 Diabetes: A Case Report, 2025

Diabetic retinopathy (DR) is the most common and severe ocular complication in diabetes. Significant advances in retinal electrophysiology have emerged in recent years in relation to diabetes-associated eye disease. Growing evidence of neuronal degeneration in DR has been established, most of which comes from electroretinography (ERG)

studies. A five-year-old male patient with type 1 diabetes mellitus (T1D), under treatment since 2021, and a 15-yearold male patient with T1D, under treatment since 2019, underwent ERG testing using the RETevalTM device (LKC Technologies, Inc., Germantown, MD, USA) and the DR program. Hemoglobin A1c (HbA1c) levels were measured at regular intervals at the outpatient clinic. The patients obtained DR protocol scores of 21.4 and 26.0, respectively. The median HbA1c during the study period was 6.2% for the first patient and 8.2% for the second. The findings suggest that RETeval could have potential clinical utility in the assessment of visual function and the early detection of diabetic eye changes.

Simó, R. Relationship between Retinal Neurodysfunction and Cognitive Impairment in Type 2 Diabetes: Results of the RECOGNISED Cross-Sectional Study, 2026

AIMS/HYPOTHESIS There are no robust, reliable and easy to administer tests to screen for mild cognitive impairment (MCI) in people living with diabetes. Since the retina is ontogenically brain-derived, we hypothesised that retinal biomarkers could be used, alone or in combination with other simple tests, to screen for MCI in people with diabetes.

METHODS Baseline data from participants screened for RECOGNISED, a Horizon 2020-funded European project, were analysed. Main eligibility criteria for RECOGNISED included age ≥65 years, type 2 diabetes of over 5 years standing, no previous history of stroke or neurodegenerative disease, and no overt diabetic retinopathy or only mild-to-moderate non-proliferative diabetic retinopathy. Baseline characteristics of participants, including scores from the Montreal Cognitive Assessment test (MoCA) and Self-Administered Gerocognitive Examination, the Diabetes Specific Dementia Risk Score (DSDRS) and ophthalmological endpoints gathered from standardised seven field colour fundus photography, spectral domain optical coherence tomography, microperimetry and a hand-held portable electroretinography device (RETeval), were obtained and used in the work presented here as potential screening predictors for presence of MCI. MCI and normocognition (NC) were determined based on a full neuropsychological test battery and the Clinical Dementia Rating score. A stepwise selection of variables, based on Akaike's information criterion, and logistic regression models for predicting MCI were undertaken. Area under the receiver-operating characteristic curve analyses were used to predict the probability of the presence of MCI as well as sensitivity and specificity cut-off points.

RESULTS A total of 313 people living with diabetes (128 with NC and 185 with MCI) were included. People with diabetes with MCI were older ($p=0.006$) and had fewer years of education ($p<0.001$), lower retinal sensitivity ($p=0.01$) and less capacity of gaze fixation ($p\leq0.001$) than those with NC. Statistically significant differences in pupillary area ratio ($p=0.002$) and photopic b-wave amplitude ($p=0.03$) were detected between people with diabetes with NC and with MCI. Multivariable logistic regression showed that the best model to identify people with diabetes with MCI was that combining retinal sensitivity, gaze fixation, photopic b-wave amplitude and pupillary size change following stimulation, years of education, DSDRS and MoCA score, with an AUC of 0.84 (sensitivity 79.9, specificity 79.0). The visuo-construction domain was the most affected in people with diabetes with MCI and its impairment was independently related to retinal sensitivity and gaze fixation.

CONCLUSIONS/INTERPRETATION The assessment of retinal neurodysfunction in combination with simple clinical variables appears useful to identify people with diabetes with MCI. This strategy could optimise current screening of MCI in people living with diabetes.

Vein Occlusion

Yasuda S. et al. Flicker electroretinograms before and after intravitreal ranibizumab injection in eyes with central retinal vein occlusion, 2015

PURPOSE: To compare the amplitudes and implicit times of the flicker electroretinograms before and after an intravitreal injection of ranibizumab (IVR) in eyes with a central retinal vein occlusion (CRVO).

METHOD: We reviewed the medical records of 15 consecutive patients who had macular oedema secondary to CRVO and had received an IVR at the Nagoya University Hospital from November 2013 to July 2014. Flicker ERGs were recorded with both the RETeval™ system and a conventional ERG system before the IVR. One month after the IVR, recordings were repeated with only the RETeval™ system.

RESULTS/ CONCLUSION: The mean implicit times of the flicker ERGs of the affected eyes recorded with the RETeval™ system were significantly longer than that of the fellow eyes (32.2 ± 2.6 msec versus 28.1 ±1.2 msec, $p < 0.001$). One month after the IVR, the implicit times of the flicker ERGs of affected eyes were significantly shortened from 32.2 ± 2.6 to 30.6 ± 2.2 msec ($p < 0.001$).

Miyata et al. Supernormal Flicker ERGs in Eyes with Central Retinal Vein Occlusion: Clinical Characteristics, Prognosis, and Effects of Anti-VEGF Agent, 2018

PURPOSE: To determine the clinical characteristics, prognosis, and effect of anti-vascular endothelial growth factor (VEGF) agents on eyes with a central retinal vein occlusion (CRVO) with and without supernormal flicker ERG amplitudes.

METHOD: Forty-eight eyes of 48 patients with a CRVO were studied. Flicker ERGs were recorded from fully dilated eyes with the RETeval system. The amplitudes and implicit times of the fundamental component were analyzed. "Supernormal flicker ERGs" were defined as those whose amplitudes were ‡117% of the unaffected fellow eyes. To determine the clinical characteristics of eyes with super-normal flicker ERG amplitudes, we separated the 48 CRVO eyes into three groups: nonischemic CRVO with supernormal flicker ERGs (Group A, n=10), nonischemic CRVO without supernormal flicker ERG (Group B, n=28), and ischemic CRVO (Group C, n=10). Then, we compared the different clinical factors among the three groups.

RESULTS/ CONCLUSION: These results indicated that the supernormal flicker ERGs can be a sign of a mild degree of ischemia, and these eyes have a better prognosis. The results also suggest that the supernormal flicker ERG may be caused by changes in the electrical activities of retinal cells following a mild increase in the VEGF levels in eyes with CRVO.

Terauchi G. et al. Retinal function determined by flicker ERGs before and soon after intravitreal injection of anti-VEGF agents, 2019

PURPOSE: To evaluate the retinal function before and soon after an intravitreal injection of an anti-vascular endothelial growth factor (anti-VEGF) agents.

METHOD: Seventy-nine eyes of 79 patients that were treated by an intravitreal injection of an anti-VEGF agent for age-related macular degeneration (AMD), diabetic macular edema (DME), or retinal vein occlusion (RVO) with macular edema (ME) were studied. The RETeval® system was used to record 28 Hz flicker electroretinograms (ERGs) from the injected and non-injected eyes before (Phase 1, P1), within 2 h after the injection (P2), and 2 to 24 h after the injection (P3).

RESULTS/ CONCLUSION: The results indicate that an intravitreal anti-VEGF injection will increase the implicit times not only in the injected eye but also in the non-injected eye soon after the intravitreal injection.

Hayreh SS. Photocoagulation for Retinal Vein Occlusion, 2021

[…] The most serious complications of central retinal vein occlusion (CRVO) and branch retinal vein occlusion (BRVO) are: (i) visual deterioration, most commonly due to macular edema, and (ii) the development of ocular neovascularization (NV), particularly neovascular glaucoma (NVG), with hazardous consequences for vision and even the eye itself. […] In CRVO, ocular NV is a complication of ischemic CRVO but not of nonischemic CRVO. […] Findings of three randomized, prospective clinical trials dealing with photocoagulation in ischemic CRVO are discussed. […]. Recent advent of intravitreal anti-VEGF and corticosteroid therapies has drastically changed the role of photocoagulation in the management of macular edema and NV in CRVO and BRVO.

Age-Related Macular Degeneration

Grewal MK, et al. A Pilot Study Evaluating the Effects of 670 nm Photobiomodulation in Healthy Ageing and Age-Related Macular Degeneration, 2020

PURPOSE: We aimed to establish the possible therapeutic effect of 670 nm light exposure on multiple visual functions and anatomical structures in healthy ageing and AMD with and without SDD to assess whether any of the tests could be reliably used in a future definitive randomized controlled trial on photobiomodulation in AMD.

METHOD: We evaluated the functional and structural effects of applying 670 nm light to 31 patients with intermediate AMD and 11 people aged 55 years or above with normal retina. The study eyes were treated daily in the morning with a 670 nm hand-held light source housed in a torch-like tube that emitted energy equivalent to 40 mW/cm2 or 4.8J/ cm2 for 2 min at the viewing aperture. Visual function in terms of best-corrected visual acuity, low luminance visual acuity, scotopic thresholds and rod-intercept time were compared between baseline and 1, 3, 6 and 12 months. Structural changes on optical coherence tomography OCT and colour photographs were also assessed.

RESULTS/CONCLUSION: In normal ageing, there was an improvement in scotopic thresholds in the group with no AMD by 1.77dB ($p = 0.03$) and no other parameters showed any clinically significant change. In eyes with intermediate AMD, there was no significant improvement in any functional or structural changes at any time point up to 12 months although the compliance was good. This pilot study shows that photobiomodulation with 670 nm has no effect in patients who have already progressed to intermediate AMD.

Grewal, MK et al. Functional Clinical Endpoints and Their Correlations in Eyes with AMD with and without Subretinal Drusenoid Deposits—a Pilot Study, 2021

PURPOSE: To evaluate functional clinical endpoints and their structural correlations in AMD, with a focus on subretinal drusenoid deposits (SDD).

METHODS: This prospective study enrolled 50 participants (11 controls, 17 intermediate AMD (iAMD) with no SDD, 11 iAMD with SDD and 11 non-foveal atrophic AMD). Participants underwent best-corrected visual acuity (BCVA), low luminance visual acuity (LLVA), low luminance questionnaire (LLQ), scotopic thresholds, rod-intercept time (RIT), photopic flicker electroretinograms and multimodal imaging. Functional and structural relationships were assessed.

RESULTS: Compared with healthy participants, BCVA, LLVA, scotopic thresholds were depressed, and RIT prolonged in iAMD patients with SDD ($p = 0.028$, $p = 0.045$, $p = 0.014$ and $p < 0.0001$ respectively). Patients with SDD also had reduced scotopic function and delayed RIT compared to iAMD without SDD ($p = 0.005$ and $p < 0.0001$). Eyes with SDD and non-foveal atrophy did not differ functionally. Nor did healthy subjects compared with iAMD without SDD. Functional parameters were significantly associated with scotopic thresholds ($r = 0.39–0.64$). BCVA, LLVA and scotopic thresholds correlated well with ONL volume, ONL thickness and choroidal thickness ($r = 0.34–0.61$).

CONCLUSION: Eyes with SDD are surrogate markers of photoreceptor abnormalities comparable with non-central atrophy and should be sub-analysed in clinical trials evaluating potential prophylactic agents to decrease the progression of AMD and may even require different therapeutic interventions.

Grewal, MK. Visual Function in Aging and Age-Related Macular Degeneration Including Subretinal Drusenoid Deposit, 2021

Age-related macular degeneration (AMD) is the leading cause of visual impairment in the developed world among people over 50 years of age. Although AMD is clinically characterised by the presence of drusen, subretinal drusenoid deposits (SDD) have also been recognized as a distinct morphological feature that confers increased risk of developing advanced AMD. To date, there has been a lack of validated biomarkers that can capture early changes in visual function that strongly correlate to the anatomical alterations which also include SDD phenotype.

This thesis aimed to explore functional and structural markers to differentiate between healthy eyes (n=11) and intermediate AMD (iAMD) with SDD (n=11) and without SDD (n=17) and non-foveal atrophic AMD (n=11). Firstly, I assessed scotopic thresholds using a novel dark-adapted chromatic (DAC) perimeter, in healthy aging and in varying AMD disease. Individuals with SDD had depressed retinal sensitivity centrally, particularly inferiorly and nasally. Functionally, eyes with SDD were comparable to eyes with non-foveal atrophy, but structurally differed in outer nuclear layer (ONL) and total retinal volumes and thicknesses. Importantly, only rod-mediated tests were able to distinguish iAMD with and without SDD.

Another aim of this thesis was to explore the efficacy of 670nm light on aging and AMD. Although an improvement in scotopic thresholds was observed in healthy aged eyes (n=4) compared to younger eyes (n=5), a pilot study conducted in 40 participants over the age 55 years (12 control, 28 with intermediate AMD) refuted any clinical benefit.

In conclusion, this thesis supports the need to re-classify the AMD severity scale by incorporating eyes with SDD as a separate group. This phenotype should be subanalysed in clinical trials evaluating potential prophylactic agents to

delay the progression. Scotopic sensitivity offers diagnostic value, but rod intercept time offers both prognostic and diagnostic value as candidate biomarkers.

Galuszka, M et al. Age-Related Macular or Retinal Degeneration? 2023

Age-related macular degeneration (AMD) is an eye disease that leads to progressive vision loss. Its prevalence has been increasing due to population aging. Previously, it was commonly believed that the disease affects the central retina, that is, the macula. However, recent studies have shown that it also involves the peripheral retina. Novel imaging techniques revealed various degenerative lesions that extend beyond the central macula. While their prevalence remains unknown, they seem to be more frequent in patients with late AMD. These findings suggest that the term “age-related retinal dysfunction” might be more adequate to describe some cases of AMD. They also raise the question about the role of electroretinography (ERG) as an objective measure of retinal function. The most common types of ERG tests used in AMD are multifocal (mfERG) and full-field ERG (ffERG). mfERG is more sensitive to macular changes, but the test is difficult to perform when fixation is unstable. On the other hand, ffERG reflects the function of the entire retina, not only the macular area. It helps assess the impact of peripheral retinal lesions and overall retinal function in patients with AMD. As ffERG results are normal in early-stage AMD, any abnormalities indicate that the disease is more severe and affects the entire retina. Anti-vascular endothelial growth factor injections improve retinal function in patients with neovascular AMD, as demonstrated by an increase in their ERG responses. More research is needed to assess the association between local and general retinal dysfunction. In this review, ffERG findings in patients with AMD are described and the usefulness of ffERG is discussed based on previous studies and cases from our own clinical practice.

Matsubara, H et al. Subclinical Ocular Changes after Intravitreal Injections of Different Anti-VEGF Agents for Neovascular Age-Related Macular Degeneration, 2023

Intraocular inflammations (IOIs) have been reported to occur after intravitreal injections of brolucizumab, and one of their causes has been suggested to be drug-specific features. We evaluated the anterior chamber by the aqueous flare value (AFV) and the retina by flicker electroretinography (ERG) after the initial intravitreal injection of aflibercept (IVA), brolucizumab (IVBr), or faricimab (IVF) for neovascular age-related macular degeneration (nAMD). The AFV and flicker ERGs were determined before, 2 weeks after, and 4 weeks after the injections in 14 eyes of 14 patients for each drug. After the injections, none of the patients had an IOI, but the AFV increased significantly in the IVA and IVF groups. The increase in the IVF group was +4.6 photon count/ms, which was significantly greater than in the other groups, but was not clinically significant. The implicit time was significantly prolonged in the IVBr group but unchanged in the IVA and IVF groups. These results suggest that brolucizumab, administered at high molar doses, may cause transient retinal disturbances that are not detectable by general ophthalmologic examinations but affect the implicit ERG times.

Glaucoma & Optic Neuropathies

Wu Z. et al. Photopic Negative Response Obtained Using a Handheld Electroretinogram Device: Determining the Optimal Measure and Repeatability, 2016

PURPOSE: This study therefore sought to determine the test-retest repeatability of the PhNR using the novel handheld ERG system under various testing conditions (including both intra- and intersession) in normal participants, and to determine the optimal measure of the PhNR for minimizing the degree of variability after normalizing its magnitude of repeatability by its EDR. It also sought to determine whether increasing the number of recordings could improve the repeatability of the PhNR.

METHOD: Multiple ERG recordings (using 200 sweeps each) were performed in both eyes of 20 normal participants at two different sessions to compare its coefficient of repeatability (CoR; where 95% of the test-retest difference is expected to lie) between different PhNR measures and under different testing conditions (within and between examiners, and between sessions).

RESULTS/ CONCLUSION: The PhNR/B ratio was the measure that minimized variability, and its measurements using a novel handheld ERG system with self-adhering skin electrodes and the protocols described in this study were comparable under different testing conditions and over multiple recordings.

The PhNR can be measured for clinical and research purposes using a simple-to-implement technique that is consistent within and between visits, and also between examiners.

Fry E.L. et al. The coma in glaucoma: Retinal ganglion cell dysfunction and recovery, 2018

PURPOSE: Retinal ganglion cell (RGC) degeneration causes vision loss in patients with glaucoma, and this has been generally considered to be irreversible due to RGC death. We question this assertion and summarise accumulating evidence that points to visual function improving in glaucoma patients with treatment, particularly in the early stages of disease. We propose that prior to death, RGCs enter periods of dysfunction but can recover with relief of RGC stress. Detecting RGC dysfunction and augmenting recovery of such 'comatosed' RGCs holds clinical potential to improve early detection of glaucoma and improve visual function.

METHOD: Aspects of RGC injury and recovery can be broadly divided into functional and structural changes. Here, clinical and pre-clinical studies that investigate changes to RGC function and structure in glaucoma are discussed. We present evidence to address three primary questions: (1) do RGCs demonstrate dysfunction prior to cell death?; (2) if so, do RGCs have the capacity recover from dysfunction?; and (3), what factors affect RGC recovery and how might this be modulated? We then highlight directions for future work.

RESULTS/CONCLUSION: While the concept of the injured ganglion cell has been present in the glaucoma literature for decades (Spaeth, 1985), we now possess the technology to interrogate RGCs experimentally at the cellular level and use these findings to develop clinically relevant tools to diagnose and treat RGC dysfunction in glaucoma. Clinical studies have identified that RGC dysfunction occurs early in both patients with OHT and glaucoma. This is detectable with electroretinography and may be reversible with reduction in IOP.

There is less evidence to suggest that reduction in IOP results in improved functional or structural outcomes commonly measured in the clinical setting including visual fields, ONH appearance and RNFL thickness. However, evidence that recovery does occur, in at least some patients, suggests that it may be possible to improve RGC function and improve vision with IOP lowering and points to the potential of other neuroprotective interventions.

Tang G. et al. Baseline Detrending for the Photopic Negative Response, 2018

PURPOSE: The photopic negative response (PhNR) of the light-adapted electroretinogram (ERG) holds promise as an objective marker of retinal ganglion cell function. We compared baseline detrending methods to improve PhNR repeatability without compromising its diagnostic ability in glaucoma.

METHOD: Photopic ERGs were recorded in 20 glaucoma and 18 age-matched control participants. A total of 50 brief, red-flashes (1.6 cd.s/m2) on a blue background (10 photopic cd/m2) were delivered using the RETeval device. Detrending methods compared were: (1) increasing the high-pass filter from 1 to 10 Hz and (2) estimating and removing the trend with an increasing polynomial (order from 1–10) applied to the prestimulus interval, prestimulus and postsignal interval, or the whole ERG signal. Coefficient of repeatability (COR%), unpaired Student's t-test, and area under the receiver operating characteristic curve (AUC) were used to compare the detrending methods.

RESULTS/ CONCLUSION: Most detrending methods improved PhNR test–retest repeatability compared to the International Society for Clinical Electrophysiology of Vision (ISCEV) recommended 0.3 to 300 Hz band-pass filter (COR% ± 200%). In particular, detrending with a polynomial (order 3) applied to the whole signal performed the best (COR% ± 44%) while achieving similar diagnostic ability as ISCEV band-pass (AUC 0.74 vs. 0.75, respectively). However, over-correcting with higher orders of processing can cause waveform distortion and reduce diagnostic ability.

Baseline detrending can improve the PhNR repeatability without compromising its clinical use in glaucoma.

Tang J. et al. A Comparison of the RETeval Sensor Strip and DTL Electrode for Recording the Photopic Negative Response, 2018

PURPOSE: To compare the RETeval sensor strip and Dawson-Trick-Litzkow (DTL) electrodes for recording the photopic negative response (PhNR) using a portable electroretinogram (ERG) device in eyes with and without glaucoma.

METHOD: Twenty-six control and 31 glaucoma or glaucoma-suspect participants were recruited. Photopic ERGs were recorded with sensor strip and DTL electrodes in random order using the LKC RETeval device.

RESULTS/ CONCLUSION: Sensor strip electrodes are a viable alternative for recording reproducible PhNRs, especially when values are normalized to the b-wave. However, DTL electrodes should be considered in cases of attenuated PhNR, or in elevated noise levels, due to its better signal-to-noise quality. Sensor strip electrodes can simplify PhNR recordings in the clinic, potentially eliminating the need for an experienced operator.

Hui F. et al. Optimizing a Portable ERG Device for Glaucoma Clinic: The Effect of Interstimulus Frequency on the Photopic Negative Response, 2018

PURPOSE: The purpose of this study was to investigate the effect of interstimulus frequency on the photopic negative response (PhNR) in glaucoma and healthy eyes. (...). Here we show the importance of considering flash interstimulus frequency when designing ERG.

METHOD: Participants (n=20 controls, n=15 glaucoma) were recruited from the glaucoma and surgical outpatient clinics at the Royal Victorian Eye and Ear Hospital. The PhNR amplitude was measured in three ways: (1) as a minimum from the baseline to trough (BT), (2) from the b-wave peak to PhNR trough (PT), and (3) as a ratio to the b-wave (ratio).

RESULTS/CONCLUSION: An interstimulus frequency of 2 Hz was optimal for recording the PhNR, creating a good balance between testing time and signal quality. A higher frequency could be used to further shorten clinical testing times; however, this may compromise its clinical utility by dampening the PhNR.

Hui F. et al. Improvement in Inner Retinal Function in Glaucoma in Response to Nicotinamide (Vitamin B3) Supplementation: A Crossover Randomized Clinical Trial, 2020

PURPOSE: To determine whether nicotinamide supplementation taken in conjunction with 48 conventional IOP-lowering therapy leads to early improvement in retinal ganglion cell 49 function in people with glaucoma.

METHOD: Crossover, double-masked, randomized clinical trial conducted between October 2017 to January 2019. Adults diagnosed and treated for primary glaucoma. Ninety-four participants assessed for study eligibility. Primary endpoint was change in inner retinal function determined a-priori as change in photopic negative response (PhNR) parameters: saturated PhNR amplitude (Vmax), ratio of PhNR/b-wave amplitude (Vmax ratio).

RESULTS/CONCLUSION: Fifty-seven participants (65.5 ± 10.0 years, 39% female) enrolled. PhNR Vmax improved beyond 95% coefficient of repeatability (COR) in 23% of participants following 12 weeks of nicotinamide versus 9% on placebo. Conversely, PhNR Vmax deteriorated in 9% on placebo and 7% on nicotinamide. Overall, Vmax improved by 14.8% [95% CI: 2.8%, 26.9%], (p=0.02) on nicotinamide and 5.2% [-4.2%, 14.6%], (p=0.27) on placebo. Vmax ratio improved on average by 12.6% [5.0%, 20.2%], (p=0.002) following nicotinamide and 3.6% [-3.4%, 10.5%], (p=0.30) on placebo. A concomitant trend for improved visual field mean deviation was observed with 27% improving ≥1dB on nicotinamide and fewer deteriorating ≥1dB (4%) compared to placebo (p=0.02). Moderate correlation was observed between PhNR and visual field change with treatment. Participants demonstrated excellent treatment adherence rates (>94%) and nicotinamide was well tolerated with minimal side effects.

Kato K. et al. Factors Affecting Photopic Negative Response Recorded with RETeval System: Study of Young Healthy Subjects, 2020

PURPOSE: To determine whether there is a significant correlation between the amplitude of the photopic negative response (PhNR) and the peripapillary retinal nerve fiber layer thickness (pRNFLT) in eyes of young, healthy subjects.

METHODS: We analyzed 136 eyes of 136 young, healthy subjects (89 males and 47 females; age, 20–29 years). The PhNRs were recorded with the RETeval system without mydriasis using red flashes on a blue background. PhNR amplitude was measured at two points: at 72 ms (P72) and at the negative trough following the b-wave (Pmin).

Univariate and multivariable linear regression analyses were performed to identify the independent variables that were significantly correlated with P72 and Pmin. The variables included age, sex, axial length, pRNFLT, intraocular pressure (IOP), a-wave amplitude, b-wave amplitude, and pupillary area during the electroretinogram recordings.

RESULTS: The amplitudes of P72 and Pmin were significantly larger in female subjects (P = 0.021 and P = 0.001, respectively). Univariate analyses showed that PhNR amplitudes were significantly correlated with pRNFLT (P72: r = 0.246, P = 0.004; Pmin: r = 0.219, P = 0.011). Female sex was significantly and negatively correlated with P72 (r = −0.206; P = 0.016) and Pmin (r = −0.271; P = 0.001). Multivariable regression analyses showed that greater pRNFLT was an independent factor significantly associated with a larger P72 (r = 0.283; P = 0.004) and Pmin (r = 0.299; P = 0.002). Female sex was an independent factor that was significantly associated with a larger Pmin (r = −0.208; P = 0.022).

^^ These findings indicate that PhNR amplitude is significantly associated with pRNFLT and female sex in young, healthy subjects.

TRANSLATIONAL RELEVANCE: The amplitude of the PhNR recorded with RETeval is smaller in subjects with thinner pRNFLT not only in glaucoma patients but also in young healthy subjects.

Kita Y et al. RETeval Portable Electroretinogram Parameters in Different Severity Stages of Glaucoma, 2020

PURPOSE: To investigate the RETeval full field electroretinogram (ERG) parameters for accuracy of separating glaucoma and normal eyes, and correlation with glaucoma severity

METHOD: Sixty-two eyes of 62 primary open-angle glaucoma patients (visual field mean deviation [MD] range: −0.44 to −31.15 dB) and 39 eyes of 39 healthy controls underwent one RETeval test (photopic negative response protocol), optical coherence tomography (OCT) imaging, and Humphrey 30-2 visual field testing

RESULTS/CONCLUSION: Significant correlations were found between the best-performing 4 RETeval ERG parameters and the glaucoma severity measures (MD and OCT thickness parameters) for all eyes, Except for P-ratio, there was no significant difference between the AUROC values of the OCT thickness parameters (range: 0.927 to 0.938) and the 4 best-performing RETeval ERG parameters (range: 0.839 to 0.905) in the early glaucoma vs. control separation. [...] differentiating the control and the moderate-to-advanced glaucoma eyes, the AUROC values of the 4 best-performing RETeval ERG parameters ranged between 0.924 and 0.958, and no significant difference was found between them and those of the OCT parameters.

Tang J. et al. Short-Term Changes in the Photopic Negative Response Following Intraocular Pressure Lowering in Glaucoma, 2020

PURPOSE: To determine whether there is a significant correlation between the amplitude of the photopic negative response (PhNR) and the peripapillary retinal nerve fiber layer thickness (pRNFLT) in eyes of young, healthy subjects.

METHODS: We analyzed 136 eyes of 136 young, healthy subjects (89 males and 47 females; age, 20–29 years). The PhNRs were recorded with the RETeval system without mydriasis using red flashes on a blue background. PhNR amplitude was measured at two points: at 72 ms (P72) and at the negative trough following the b-wave (Pmin). Univariate and multivariable linear regression analyses were performed to identify the independent variables that were significantly correlated with P72 and Pmin. The variables included age, sex, axial length, pRNFLT, intraocular pressure (IOP), a-wave amplitude, b-wave amplitude, and pupillary area during the electroretinogram recordings.

RESULTS: The amplitudes of P72 and Pmin were significantly larger in female subjects (P = 0.021 and P = 0.001, respectively). Univariate analyses showed that PhNR amplitudes were significantly correlated with pRNFLT (P72: r = 0.246, P = 0.004; Pmin: r = 0.219, P = 0.011). Female sex was significantly and negatively correlated with P72 (r = −0.206; P = 0.016) and Pmin (r = −0.271; P = 0.001). Multivariable regression analyses showed that greater pRNFLT was an independent factor significantly associated with a larger P72 (r = 0.283; P = 0.004) and Pmin (r = 0.299; P = 0.002). Female sex was an independent factor that was significantly associated with a larger Pmin (r = −0.208; P = 0.022).

CONCLUSIONS: These findings indicate that PhNR amplitude is significantly associated with pRNFLT and female sex in young, healthy subjects.

TRANSLATIONAL RELEVANCE: The amplitude of the PhNR recorded with RETeval is smaller in subjects with thinner pRNFLT not only in glaucoma patients but also in young healthy subjects.

Bindiganavale, MP. Development and Implementation of a Handheld Pupillometer for Detection of Optic Neuropathies, 2021

PURPOSE: Quantitative pupillometry has utility in research settings for measuring optic nerve and autonomic function. We configured a portable device to perform quantitative pupillometry with application to detecting unilateral optic neuropathies in the clinical setting.

METHODS: Light stimuli were delivered, and pupil diameter responses recorded using customized software implemented on a commercial portable electroretinography device. Increasing pupillary constriction occurred with increasing duration and intensity of full field blue light (470 nm) stimuli in healthy subjects. Flashes of 1 s dim (50 cd/m2) and bright (316 cd/m2) blue light were administered to both eyes of subjects with unilateral optic neuropathies (n = 10) and controls (n = 5). Maximum pupillary constriction (Cmax) for each stimulus was compared between control eyes and optic neuropathy eyes. Cmax for the inter-eye difference curve (Cdiffmax) was compared between control and optic neuropathy subjects.

RESULTS: The pupil protocol lasted 15 minutes and was well tolerated by subjects. Cmax for bright and dim stimuli was reduced in eyes with optic neuropathy compared to fellow and control eyes ($p < .0005$ for all). Inter-eye Cdiffmax was larger in optic neuropathy subjects than control subjects for both dim and bright stimuli ($p = .002$, <0.0005). There was no overlap between groups for Cmax and Cdiffmax for either stimulus.

CONCLUSIONS: A portable pupillometer was implemented on a commercial portable electroretinography platform and applied in a pilot manner to subjects with and without unilateral optic neuropathies. Optic neuropathy eyes were distinguished from non-optic neuropathy eyes both within and between subjects.

Kong, A. Asymmetric Functional Impairment of ON and OFF Retinal Pathways in Glaucoma, 2021

PURPOSE: To investigate ON-pathway versus OFF-pathway dysfunction in glaucoma using handheld electroretinography (ERG) with a temporally modulated sinusoidal flicker stimulus.

METHODS: Fifty-nine participants accounting for 104 eyes, comprised of 19 control eyes, 26 glaucoma suspect eyes, and 59 glaucoma eyes. Participants underwent portable ERG testing, which included the photopic flash, photopic flicker, photopic negative response stimulus, ON-OFF stimulus, and a custom-written sinusoidal flicker stimulus that was modulated from 50 to 0.3 Hz. The ERG response amplitudes were measured by the handheld ERG. For the custom-written sinusoidal flicker stimulus, we derived and compared the log10 first harmonic frequency response amplitudes. Patient discomfort and fatigue after ERG testing were rated on a scale from 1 to 5

RESULTS: Baseline demographics were not significantly different between groups, except for ocular characteristics. Analysis was performed adjusting for participant age, sex, race, and dilation status, and the sinusoidal frequency responses were stratified at 10 Hz because higher frequencies are associated with the OFF-pathway, whereas lower frequencies are associated with the ON-pathway. After stratification, glaucoma eyes showed an adjusted decrease of 32.1% at frequencies of more than 10 Hz (95% confidence interval [CI], −51.8% to −4.1%; P = 0.03). For 10 Hz stimulus frequencies or less, an adjusted 11.5% reduction was found (95% CI, −39.5% to 29.1%; P = 0.50). Glaucoma suspect eyes did show a decreased response, but this was not significant at either frequency range. When comparing handheld ERG with traditional visual field assessments, participants found the handheld ERG to result in much less discomfort and fatigue.

CONCLUSIONS: Our finding that glaucoma participants showed greater decreases in ERG response at higher frequencies supports the hypothesis that the OFF-pathway may be more vulnerable in human glaucoma. Using a handheld ERG device with a sinusoidal flicker stimulus may provide an objective assessment of visual function in glaucoma.

Diao, T. Comparison of Machine Learning Approaches to Improve Diagnosis of Optic Neuropathy Using Photopic Negative Response Measured Using a Handheld Device, 2021

The photopic negative response of the full-field electroretinogram (ERG) is reduced in optic neuropathies. However, technical requirements for measurement and poor classification performance have limited widespread clinical application. Recent advances in hardware facilitate efficient clinic-based recording of the full-field ERG. Time series classification, a machine learning approach, may improve classification by using the entire ERG waveform as the input. In this study, full-field ERGs were recorded in 217 eyes (109 optic neuropathy and 108 controls) of 155 subjects. User-defined ERG features including photopic negative response were reduced in optic neuropathy eyes ($p < 0.0005$, generalized estimating equation models accounting for age). However, classification of optic neuropathy based on user-defined features was only fair with receiver operating characteristic area under the curve ranging between 0.62 and 0.68 and F1 score at the optimal cutoff ranging between 0.30 and 0.33. In comparison, machine learning classifiers using a variety of time series analysis approaches had F1 scores of 0.58–0.76 on a test data set. Time series classifications are promising for improving optic neuropathy diagnosis using ERG waveforms. Larger sample sizes will be important to refine the models.

Rufus-Toye R. Measurement of electroretinogram responses in OPA1-associated autosomal dominant optic atrophy using a handheld device, 2022

PURPOSE: [...]. In this study, we explored the potential of using a handheld ERG device (RETeval®) to measure ERG responses in a cohort of patients with ADOA carrying pathogenic OPA1 mutations.

METHODS: The Ganzfeld photopic ERG was recorded in 15 individuals with OPA1-associated ADOA in response to series of flashes (200, automatically adjusted in intensity to pupil diameter) using the RETeval® handheld ERG device and skin electrodes. Both visual acuity measurements, and optical coherence tomography ganglion cell layer (GCL) and retina nerve fibre layer (RNFL) thicknesses were recorded to explore correlation with ERG parameters.

RESULTS: There was a significant correlation between LogMAR visual acuity and both the a-wave (ρ = -0.60, p = 0.02, n = 15) and b-wave (ρ = -0.54, p = 0.04, n = 15) peak times. There was no significant correlation between a-wave and b-wave peak times with the OCT structural parameters that were analysed.

CONCLUSION: In patients with OPA1-associated ADOA, a-wave and b-wave peak times correlated negatively with LogMAR visual acuity, independent of the effects of age. The pathophysiological relevance of these findings requires further investigation in a larger patient cohort.

Igawa Y. Early changes in photopic negative response in eyes with glaucoma with and without choroidal detachment after filtration surgery, 2022

PURPOSE: To evaluate the electroretinographic (ERG) changes in the early postoperative period following glaucoma filtration surgery, and its relationship with choroidal detachment (CD)..

METHODS: This retrospective observational single-centre study included 57 consecutive patients with primary open-angle glaucoma who underwent unilateral glaucoma filtration surgery. The patients were divided into two groups according to the presence or absence of CD. ERG components, including the photopic negative response (PhNR), a-wave and b-wave were compared before and after surgery using skin electrodes.

RESULTS: There were 46 patients in the non-CD group and 11 in the CD group. ERG was recorded within 5.1 (2.1 to 8.1) (mean (95% CI)) days after surgery. In the non-CD group, the PhNR amplitude, PhNR/b-wave amplitude ratio and PhNR implicit time improved significantly after surgery (p=0.008, 0.002 and 0.039, respectively). In the CD group, the amplitude of the PhNR, a-wave and b-wave were significantly deteriorated after surgery (p=0.002, 0.001 and 0.001, respectively). Postoperative intraocular pressure (IOP) (p=0.031) and postoperative CD (p<0.001) were significantly associated with change in the PhNR amplitude in the univariate models. In the multivariate analysis, severe CD (stage 3) cases tended to be deteriorated more.

CONCLUSION: Even in the early postoperative period within several days, the PhNR amplitude increased with IOP lowering following filtration surgery in the absence of CD. The presence of CD may arrest the improvement of the retinal ganglion cell function. The present results enhance understanding the structural and functional recovery after glaucoma surgery and the role of postoperative CD.

Yamashita et al. Photopic negative response recorded with RETeval system in eyes with optic nerve disorders, 2022

PURPOSE: The purpose of this study was to determine the usefulness of ERGs recorded with the RETeval system in diagnosing optic nerve diseases.

METHODS: Forty-eight patients with optic nerve disorders, including optic neuritis, ischemic optic neuropathy, traumatic optic neuropathy, and dominant optic atrophy, and 36 normal control subjects were studied. The amplitudes of the photopic negative response (PhNR) were recorded with the RETeval system without mydriasis. The circumpapillary retinal nerve fiber layer thickness (cpRNFLT) was determined by optical coherence tomography (OCT). The significance of the correlations between the PhNR and cpRNFLT parameters were determined, and the receiver operating curve (ROC) analyses were performed for the PhNR and cpRNFLT.

RESULTS: Patients with optic nerve disorders had significantly smaller PhNRs compared to the control subjects (P = 0.001). The ROC analyses indicated that both PhNR and cpRNFLT had comparable diagnostic abilities of detecting optic nerve disorders with PhNR at 0.857 and cpRNFLT at 0.764. The PhNR components recorded with the RETeval system have comparable diagnostic abilities as the cpRNFLT in diagnosing optic nerve disorders.

Pojda-Wilczek et al. Phenotypic Variation of Autosomal Recessive Leber Hereditary Optic Neuropathy (arLHON) in One Family, 2022

ABSTRACT: Leber hereditary optic neuropathy (LHON) is a rare disease with a prevalence of 1 in 25,000 births. LHON usually presents in young males, with painless loss of visual acuity in one or both eyes. Recently an autosomal recessive form of the disease (arLHON or LHONAR) has been described, which is caused by a biallelic mutation in the DNAJC30 gene (usually a missense mutation c.152A>G). The phenotypic and clinical characteristics of patients with arLHON are similar to those of mtLHON, but some differences have been described. Therapy is problematic and challenging. This paper describes clinical and electrophysiological findings in one family (three children and two parents) with arLHON and emphasizes the role of Photopic Negative Response Electroretinography, which provides objective measurement of retinal ganglion cells function. In Leber hereditary optic neuropathy, abnormal retinal ganglion cells function can be found in both eyes, even if visual acuity loss only occurs in one eye. Early clinical diagnosis, confirmed by genetic analysis, may be the key to sight-preserving treatment.

Bekollari et al. Investigating the Structural and Functional Changes in the Optic Nerve in Patients with Early Glaucoma Using the Optical Coherence Tomography (OCT) and RETeval System, 2023

ABSTRACT: The present manuscript introduces an investigation of the structural and functional changes in the optic nerve in patients undergoing glaucoma treatment by comparing optical coherence tomography (OCT) measurements and RETeval system parameters. For such a purpose, 140 eyes were examined at the Ophthalmology Clinic of the “Elpis” General Hospital of Athens between October 2022 and April 2023. A total of 59 out of 140 eyes were from patients with early glaucoma under treatment (case group), 63 were healthy eyes (control group) and 18 were excluded. The experimental measurements were statistically analyzed using the SPSS software package. The main outcomes are summarized below: (i) there was no statistical difference between the right and left eye for both groups, (ii) statistical differences were found between age interval subgroups (30–54 and 55–80 years old) for the control group, mainly for the time response part of the RETeval parameters. Such difference was not indicated by the OCT system, and (iii) a statistical difference occurred between the control and case group for both OCT (through the retinal nerve fiber layer–RNFL thickness) and the RETeval parameters (through the photopic negative response–PhNR). RNFL was found to be correlated to b-wave (ms) and W-ratio parameters. In conclusion, the PhNR obtained by the RETeval system could be a valuable supplementary tool for the objective examination of patients with early glaucoma.

Hidaka, T et al. Evaluation of inner retinal function at different stages of primary open angle glaucoma using the photopic negative response (PhNR) measured by RETeval electroretinography, 2023

PURPOSE: To investigate the objective function of the inner retinal layer in each stage of primary open angle glaucoma (POAG) using the photopic negative response (PhNR) measured by RETeval full-field electroretinography (ERG), and to identify which PhNR parameter is the most useful.

METHODS: Ninety eyes of 90 patients with POAG (30 with mild POAG (mean deviation (MD) ≥ -6 dB) and 60 with moderate-to-advanced POAG (MD < -6 dB)) and 76 eyes of 76 control cases were examined. We investigated six PhNR parameters and their relationships with the results of the Humphrey 30-2 visual field test and the thickness of the circumpapillary retinal nerve fiber layer (cpRNFL) obtained from optical coherence tomography. The following PhNR parameters were assessed: base-to-trough (BT), peak-to-trough (PT), 72msPhNR, the W-ratio, P-ratio, implicit time (IT), and a-wave and b-wave amplitudes on ERG.

RESULTS: All PhNR parameters other than IT significantly differed between the all POAG (all stages) and control groups and between the moderate-to-advanced POAG and control groups. BT and 72msPhNR in the mild POAG group, significantly differed from those in the control group. Regarding the relationships between PhNR parameters and the visual field and between these parameters and cpRNFL thickness, correlations were observed between all PhNR parameters, except PT and IT, and both the visual field and cpRNFL thickness in the all and moderate-to-advanced POAG groups. 72msPhNR correlated with cpRNFL thickness in the mild POAG group. The area under the receiver operating characteristic curve was greater for BT than for the other PhNR parameters in both the mild and moderate-to-advanced POAG groups. The discriminant linear function for examining the presence or absence of POAG and the threshold for diagnosis were quantitatively obtained as follows. Regarding BT: discriminant = 0.505 × BT + 2.017; threshold = positive for POAG, negative for no POAG; correct answer rate = 80.7%. Concerning 72msPhNR: discriminant = 0.533 × 72msPhNR + 1.553; threshold = positive for POAG and negative for no POAG; correct answer rate = 77.1%.

CONCLUSION: RETeval-measured PhNR parameters were useful for an objective evaluation of visual function in moderate-to-advanced POAG. BT appeared to be the most diagnostically useful parameter.

Bekollari, M et al. Computer-Aided Discrimination of Glaucoma Patients from Healthy Subjects Using the RETeval Portable Device, 2024

Glaucoma is a chronic, progressive eye disease affecting the optic nerve, which may cause visual damage and blindness. In this study, we present a machine-learning investigation to classify patients with glaucoma (case group) with respect to normal participants (control group). We examined 172 eyes at the Ophthalmology Clinic of the "Elpis" General Hospital of Athens between October 2022 and September 2023. In addition, we investigated the glaucoma classification in terms of the following: (a) eye selection and (b) gender. Our methodology was based on the features extracted via two diagnostic optical systems: (i) conventional optical coherence tomography (OCT) and (ii) a modern RETeval portable device. The machine-learning approach comprised three different classifiers: the Bayesian, the Probabilistic Neural Network (PNN), and Support Vectors Machines (SVMs). For all cases examined, classification accuracy was found to be significantly higher when using the RETeval device with respect to the OCT system, as follows: 14.7% for all participants, 13.4% and 29.3% for eye selection (right and left, respectively), and 25.6% and 22.6% for gender (male and female, respectively). The most efficient classifier was found to be the SVM compared to the PNN and Bayesian classifiers. In summary, all aforementioned comparisons demonstrate that the RETeval device has the advantage over the OCT system for the classification of glaucoma patients by using the machine-learning approach.

Ji, P. Artificial Intelligence in Glaucoma: A New Landscape of Diagnosis and Management, 2024

Glaucoma refers to a spectrum of progressive optic neuropathies and remains the leading cause of irreversible blindness worldwide. Its insidious onset poses serious challenges to conventional diagnostic methods and clinicians striving to detect early-stage disease for timely and effective intervention. Artificial intelligence (AI) has demonstrated its ability to process and analyze large datasets which can help identify subtle changes in early glaucomatous clinical presentation. This study reviews the current state of AI utilization in glaucoma and elucidates the strengths and limitations of existing approaches. We dissect the role of AI in various domains: enhancing early detection and diagnosis, monitoring disease progression, and refining treatment strategies to optimize patient outcomes. Furthermore, we address the ethical, legal, and social implications, alongside the inherent limitations of AI in the clinical setting. Despite these challenges, AI holds transformative potential for glaucoma management. Future directions emphasize the need for interdisciplinary collaboration, advanced and explainable algorithm development, and equitable healthcare access to fully realize the promise of AI in combating this vision-threatening condition.

Kumar, A. Diagnostic Performance of a Handheld Electroretinography Test for Glaucoma, 2025

PURPOSE: To evaluate the diagnostic performance of a sinusoidal flicker stimulus test at various frequencies using a handheld electroretinography (ERG) device in glaucoma versus control participants.

DESIGN: A cross-sectional study conducted between June 2019 and October 2022 at the University of California, San Francisco.

PARTICIPANTS: Participants with glaucoma were recruited from glaucoma clinics if they had a diagnosis of open-angle glaucoma, as demonstrated by optic nerve damage or reproducible visual field defects. Control participants had normal optic nerves and intraocular pressures of >=21 mmHg and were recruited from optometry clinics.

METHODS: The RETeval device (LKC Technologies), a handheld ERG recording system, was used to administer a sinusoidal flicker stimulus modulated at 14 frequencies from 1 to 50 Hz, and the first harmonic frequency response amplitudes were collected. Logistic regression models with glaucoma diagnosis as the outcome were trained using data from 67% of participants; models were then tested on the remaining 33%.

MAIN OUTCOME MEASURES: Receiver operating characteristic curves demonstrating model performance on the testing set were generated, and area under the receiver operating characteristic curve (AUC) was calculated. The improved DeLong algorithm was used to compare diagnostic performance of the models and differences in performance in dilated versus nondilated eyes.

RESULTS: The study included 117 eyes from 72 participants (18 control, 54 glaucoma; mean age [standard deviation {SD}] ¼ 70.4 [12.2] years; 51.4% female). Among glaucomatous eyes, average (SD) mean deviation was 4.61 (5.55) decibels. In a model assessing the combined effects of amplitude responses across all frequencies, the AUC was 0.57 (95% confidence interval [CI]: 0.37e0.78). However, in a model focusing on frequencies of 30 Hz, where the OFF pathway may be more affected, the AUC improved to 0.81 (95% CI: 0.66e0.97). In this higher frequency model, sensitivity was 80% and specificity was 74% at the Youden J cutoff.

CONCLUSIONS: These findings provide evidence of the potential use of handheld ERG in diagnosing glaucoma by assessing retinal amplitude responses to sinusoidal flicker stimuli at frequencies between 30 and 50 Hz. This supports the hypothesis that the OFF pathway may be more vulnerable in glaucoma.

Tachibana, M. Case of autosomal dominant optic atrophy with relatively good visual function, 2025

BACKGROUND: Dominant optic atrophy (DOA) is an inherited optic neuropathy caused by mutations of the OPA1 gene. Patients with DOA have a gradual loss of vision that is often detected in early life. While most cases stabilize at around a decimal best-corrected visual acuity (BCVA) of 0.1, some show mild impairments without visual field abnormalities. This then makes the diagnosis of DOA difficult. We report our longitudinal findings of a 56-year-old man with autosomal dominant DOA whose visual functions remained relatively good and genetic testing was needed for the diagnosis of DOA.

CASE PRESENTATION: The patient was first examined 7 years earlier when he was 49-year-old at the Saitama Medical University Hospital. His major complaint was blurred vision. He had no medical or family history of ocular disorders, and his decimal BCVA was 1.0 (Snellen 20/20) in both eyes (OU). The intraocular pressure (IOP) was 13.7 mmHg in the right eye and 14.0 mmHg in the left eye. Slit-lamp examination revealed mild cataracts OU, and fundus examination showed temporal pallor of the optic discs OU. Humphrey visual field analyzer (HFA) standard 30 – 2 white-on-white perimetry indicated that the sensitivity was not reduced. Five years later, the patient returned for further examination because his vision had worsened. The decimal BCVA was 0.8 in the right eye and 0.6 in the left eye, and the IOP was within normal limits OU. The critical fusion frequency (CFF) was 30 Hz in the right eye and 31 Hz (normal values > 39 Hz) in the left eye. Slit-lamp examination and ophthalmoscopy showed no intraocular changes. Optical coherence tomography (OCT) showed a thinning of the retinal nerve fiber layer temporal to the optic disc. The contrast sensitivity was slightly decreased in both eyes, and the Panel D-15 color vision test was normal. Goldmann visual field testing with HFA SITA standard 10 – 2 and 24 – 2 white-on-white perimetry showed no obvious scotomas. However, HFA SITA standard 24 – 2 blue-on-yellow perimetry showed a diffuse decrease of sensitivity. Full-field and focal macular electroretinograms (ERGs) were normal in both eyes. Genetic testing was performed with the patient's consent, and next generation sequencing analysis identified a new heterozygous c.2331+2T>G variant in the OPA1 gene (NM_130837.3). At the final follow-up examination at age 55 years, the decimal BCVA was still relatively good at 0.8 in the right eye and 0.6 in the left eye.

CONCLUSIONS: These findings indicate that relatively good visual function can be maintained until the late middle age in patients with DOA, and genetic testing should be considered when circumpapillary RNFL thinning is observed, even in patients with relatively good visual acuity.

Ha, M. Effects of nicotinamide supplementation in normal-tension glaucoma: a crossover placebo-controlled randomised clinical trial, 2025

BACKGROUND/AIMS The neuroprotective effect of nicotinamide (NAM) supplementation has been demonstrated in both animal models and clinical trials. We conducted a trial to assess whether oral NAM improves retinal function in normal-tension glaucoma (NTG) participants receiving intraocular pressure (IOP)lowering therapy.

METHODS Fifty-three NTG participants (untreated IOP ≤18 mm Hg) were enrolled in a double-masked, placebo-controlled crossover randomised clinical trial. Participants were randomly assigned to receive either oral placebo or NAM, followed by crossover without a washout period. Each treatment was administered for 12 weeks (NAM/placebo 1 g/day for 6 weeks, then 2 g/ day for the subsequent 6 weeks). Retinal function was evaluated using full-field electroretinography and visual field testing.

RESULTS After 12 weeks, the amplitude changes of the photopic negative response in peak-to-trough (PhNRPT) and the B-wave were significantly greater in the NAM group (3.121±3.968 and 2.112±3.220 µV, respectively) compared with the placebo group (0.996±4.190 and 0.305±3.279 µV, respectively; p=0.045 and p=0.032). PhNRPT improved beyond twice the 95% coefficient of variation in 29.0% of the NAM group and 19.3% of the placebo group. No significant intergroup differences were observed in changes in mean deviation, pattern SD or visual field index after 12 weeks.

CONCLUSION Oral NAM supplementation in NTG participants induced functional improvement, as measured by PhNRPT and B-wave amplitude. Given that NTG is characterised by lower IOP, which may show a weaker correlation with electrophysiological activity and a slower progression rate compared with high-tension glaucoma, further long-term studies are needed to clarify the effects of NAM in this population..

General Pediatric & Hereditary Disease Applications

Eda S. et al. A Case of Hydranencephaly in Which Ophthalmic Examinations Were Performed, 2016

PURPOSE: We performed ophthalmic examinations, including optical coherence tomography (OCT), on a case diagnosed with hydranencephaly

METHOD: This case involved a female infant born at the gestational age of 35 weeks and 4 days, with the birth weight of 2,152 g, who was one of monochorionic diamniotic twins, and the identical twin died in utero at the gestational age of 24 weeks. After that, examination by fetal echo indicated that she had microcephaly and ventriculomegaly. Postnatal magnetic resonance imaging (MRI) of her head indicated microcephaly and significant enlargement of the lateral ventricle on both sides, with no obvious signs of elevated intracranial pressure. Ophthalmic examinations indicated that both of her eyes had slight light reflex, attributed to optic nerve atrophy. Examination by use of a hand-held OCT system indicated a layered structure of the retina and thinning of the ganglion cell layer. Flicker electroretinogram (ERG) examination by use of a hand-held ERG system indicated an almost normal wave. However, no clear visual reaction was observed when she was 10 months old.

RESULTS/ CONCLUSION: Our findings in this case of hydranencephaly revealed that even though the outer layer functions of the patient's retina were maintained, extensive damage to her cerebral cortex resulted in poor visual function.

Nakamura, N. et al. Evaluation of cone function by a handheld non-mydriatic flicker electroretinogram device, 2016

PURPOSE: Determine whether a new, handheld, portable ERG device, RETeval™, can be used to screen patients for cone dysfunction.

METHOD: Thirty-five eyes of 35 patients who had reduced cone responses ascertained by a conventional ERG system using contact lens electrodes were studied. The causative diseases included achromatopsia, cone dystrophy, cone-rod dystrophy, retinitis pigmentosa, choroidal dystrophy, autoimmune retinopathy, and Stargardt disease. The flicker ERGs were recorded with the RETeval™ under undilated conditions with skin electrodes (stimulus strength, 3.0 cd·s/m2; frequency, 28.3 Hz), and the responses were compared to that of 50 healthy eyes.

RESULTS/ CONCLUSION: The RETeval™ has a potential of being used to screen for cone dysfunction. The entire examination takes <5 minutes and does not require pupil dilatation or a contact lens electrode. Although the flicker responses do not provide information on the scotopic functions, the RETeval™ device can be used to determine which patients require additional full-field ERG testing with dilated pupils under both scotopic and photopic conditions.

Grace S.F. et al. Nonsedated handheld electroretinogram as a screening test of retinal dysfunction in pediatric patients with nystagmus, 2017

PURPOSE: To assess the feasibility, sensitivity, and specificity of nonsedated handheld cone flicker electroretinogram (ERG) as a screening tool to detect retinal disfunction in children with nystagmus.

METHOD: A total of 71 children were enrolled.

(…) three age-matched groups: normal, nystagmus with a retinal dystrophy, and nystagmus without a retinal dystrophy. Unsedated 30 Hz cone flicker ERG responses were obtained using a handheld device (RETeval) from both eyes of each patient using skin electrode sensors after pupillary dilation. (…) children were dilated because the device's pupil-tracking function requires cooperative fixation during examination to deliver constant retinal luminance.

(…) amplitudes and implicit times were successfully obtained in 65 (92%): 31 (mean age SD, 5.6 2.7 years; range, 1-12 years) without nystagmus and 34 with nystagmus.

RESULTS/CONCLUSION: Unsedated handheld cone flicker ERG is a feasible screening test that effectively detects retinal dysfunction in children with nystagmus. In conjunction with clinical findings, the test helps reduce the need for sedated ERG in children.

Liu H. et al. Evaluation of light- and dark-adapted ERGs using a mydriasis-free, portable system: clinical classifications and normative data, 2018

PURPOSE: The purpose of this study was to determine the intra-visit reliability and diagnostic capability of a handheld, mydriasis-free ERG, RETeval, in comparison with the standard clinical ff-ERG by measuring responses recommended by the International Society for Clinical Electrophysiology of Vision (ISCEV). Assessing the diagnostic accuracy of the RETeval was the primary question of this study.

METHOD: 35 patients recruited (median age = 17, range 11 months–69 years) who had undergone a clinical ff-ERG according to ISCEV standards. Fifty-seven control participants (median age = 22, range 8–65 years) with no known retinal disease were recruited from the general population and underwent RETeval ERG.

RESULTS/CONCLUSION: Our study supports the finding that RETeval has a reasonable diagnostic accuracy in comparison with the clinical ff-ERG while exhibiting a high degree of sensitivity (1.00) and specificity (0.82).

The portable ERG possesses remarkable clinical reliability given adequate testing compliance, as the results demonstrated reproducibility among the control participants as well as their patient counterparts.

Ji X. et al. Hand-held, dilation-free, electroretinography in children under 3 years of age treated with vigabatrin, 2019

PURPOSE: The anti-epileptic drug vigabatrin is associated with reduction in light-adapted 30-Hz flicker electroretinogram (ERG) amplitude. Ophthalmological assessments, including ERGs, monitor retinal health during vigabatrin treatment. RETeval is a hand-held ERG device adapted for dilation-free ERG assessment. To evaluate the usefulness of RETeval for vigabatrin ERG assessment, we evaluated intra-visit reliability and clinical feasibility of RETeval ERG assessment in children under 3 years of age undergoing vigabatrin treatment.

METHOD: In this prospective study, children underwent 30-Hz flicker ERG assessment with RETeval before routine vigabatrin monitoring including sedated-ERG using the Espion E2 Colour Dome.

RESULTS/CONCLUSION: RETeval demonstrated high intra-visit reliability with responses consistent with the standard Espion ERG. RETeval may be beneficial for assessment of retinal toxicity in young children treated with vigabatrin.

Mahroo O. et al. Comparison of peak times of photopic flicker electroretinogram responses recorded using conventional and portable systems in Birdshot chorioretinopathy, 2019

PURPOSE: Assessing disease activity in Birdshot uveitis can be challenging. The peak time of the 30 Hz flicker photopic electroretinogram (ERG) was shown to be sensitive for detecting retinal dysfunction. ERG testing is not readily available in many eye units. We investigated use of a portable device to obtain recordings in the clinic setting and compared these with conventional recordings.

METHOD: Patients underwent testing with the portable device (RETeval, LKC Technologies) and conventional equipment (Espion ColorDome, Diagnosys). For portable recordings pupils were undilated and skin electrodes used; for conventional recordings a conductive fibre electrode was used with mydriasis. Flicker ERG peak times were recorded and were deemed abnormal if they exceeded the 95th centile from a healthy cohort (>190 healthy volunteers).

RESULTS/CONCLUSION: 18 patients with Birdshot uveitis underwent recordings. Recordings with the portable device took c. 3 min and were well-tolerated. Mean (SD) age was 56.3 (12.8) years. For portable recordings, mean (SD) peak times were 30.1 (3.7) and 30.2 (3.9) ms for right and left eyes respectively. For conventional recordings mean (SD) peak times were 31.4 (3.9) and 31.8 (4.0) ms respectively. Peak times were significantly shorter with the portable device ($p = 0.026$ and 0.002 for right and left eyes). Correlation between devices was high (0.83 and 0.89 for right and left eyes) and highly significant ($p < 0.0001$). Strength of agreement between the two methods was good (kappa statistic 0.64; 95% CI, 0.36-0.92).

Correlation between the portable and conventional ERG recordings was high with a good level of agreement. Recordings were rapid and well-tolerated. There were significant differences in peak times between the two methods highlighting the importance of normative data specific to each device.

Osigian C.J. et al. Assessing nonsedated handheld cone flicker electroretinogram as a screening test in pediatric patients: comparison to sedated conventional cone flicker electroretinogram, 2019

PURPOSE: To assess the RETeval (LKC Technologies, Gaithersburg, MD) handheld electroretingram (ERG) device as a screening tool for cone dysfunction in pediatric patients by comparing it to conventional ERG.

METHOD: Patients scheduled for ERG under general anesthesia (GA) underwent three tests: (1) RETeval standard 30 Hz cone flicker ERG using skin electrodes prior to GA, (2) E3 Diagnosys (Diagnosys LLC, Lowell, MA) conventional complete standard protocol full-field ERG using bipolar contact lens electrodes and handheld stimulus under GA, and (3) repeat RETeval testing under GA. The 30 Hz cone flicker amplitudes and implicit times from the three methods were compared. Negative and positive predictive values were calculated by applying a previously established 5 mV amplitude cut-off.

RESULTS/ CONCLUSION: Thirty patients ≤ 18 years of age were enrolled. Impaired conventional ERGs were found in 18 patients. Compared to conventional ERG under GA, RETeval cone flicker amplitudes were smaller before GA (mean difference, -42.2 ± 45.3 mV) and under GA (-37.1 ± 44.5 mV), likely due to skin electrode; and implicit times were shorter before GA (-1.06 ± 2.83 ms) and longer under GA (1.28 ± 4.12 ms), likely due to GA. Comparing RETeval responses before and under GA, the amplitudes were lower (-3.05 ± 6.82 mV), and implicit times were shorter (-2.25 ± 3.28 mV) before GA. Overall, the positive predictive value of the RETeval was 85%; the negative predictive value, 90%.

The unsedated handheld RETeval 30 Hz cone flicker ERG is a feasible screening test for detecting cone dysfunction in pediatric patients. Full-protocol ERG is needed when screening ERG is reduced, equivocal, or clinically warranted.

Lang E. et al. Genotype–Phenotype Spectrum in Isolated and Syndromic Nanophthalmos, 2020

PURPOSE: To (i) describe a series of patients with isolated or syndromic nanophthalmos with the underlying genetic causes, including novel pathogenic variants and their functional characterization and (ii) to study the association of retinal dystrophy in patients with MFRP variants, based on a detailed literature review of genotype–phenotype correlations.

METHODS: Patients with nanophthalmos and available family members received a comprehensive ophthalmological examination. Genetic analysis was based on whole exome sequencing and variant calling in core genes including MFRP, BEST1, TMEM98, PRSS56, CRB1, GJA1, C1QTNF5, MYRF and FAM111A. A minigene assay was performed for functional characterization of a splice site variant.

RESULTS: Seven patients, aged between three and 65 years, from five unrelated families were included. Novel pathogenic variants in MFRP (c.497C>T, c.899-3C>A, c.1180G>A), and PRSS56 (c.1202C>A), and a recurrent de novo variant in FAM111A (c.1706G>A) in a patient with Kenny–Caffey syndrome type 2, were identified. In addition, we report co-inheritance of MFRP-related nanophthalmos and ADAR-related Aicardi–Gouti_eres syndrome.

CONCLUSION: Nanophthalmos is a genetically heterogeneous condition, and the severity of ocular manifestations appears not to correlate with variants in a specific gene. However, retinal dystrophy is only observed in patients harbouring pathogenic MFRP variants. Furthermore, heterozygous carriers of MFRP and PRSS56 should be screened for the presence of high hyperopia. Identifying nanophthalmos as an isolated condition or as part of a syndrome has implications for counselling and can accelerate the interdisciplinary care of patients.

Özmert E. et al. Management of retinitis pigmentosa by Wharton's jelly derived mesenchymal stem cells: preliminary clinical results, 2020

PURPOSE: The aim of this study is to determine if umbilical cord Wharton's jelly derived mesenchymal stem cells implanted in sub-tenon space have beneficial effects on visual functions in retinitis pigmentosa patients by reactivating the degenerated photoreceptors in dormant phase.

METHOD: This prospective, open-label, phase-3 clinical trial was conducted between April of 2019 and October of 2019 at Ankara University Faculty of Medicine, Department of Ophthalmology. 32 RP patients (34 eyes) were included in the study. The patients were followed for 6months after the Wharton's jelly derived mesenchymal stem cell administration, and evaluated with consecutive examinations. All patients underwent a complete routine ophthalmic examination, and best corrected visual acuity, optical coherens tomography angiography, visual field, multifocal and full-field electroretinography were performed. The quantitative results were obtained from a comparison of the pre-injection and final examination (6th month) values.

RESULTS/ CONCLUSION: RP is a genetic disorder that can result in blindness with outer retinal degeneration. Regardless of the type of genetic mutation, sub-tenon Wharton's jelly derived mesenchymal stem cell administration appears to be an effective and safe option. There are no serious adverse events or ophthalmic / systemic side effects for 6months follow-up. Although the long-term adverse effects are still unknown, as an extraocular approach, subtenon implantation of the stem cells seems to be a reasonable way to avoid the devastating side effects of intravitreal/submacular injection. Further studies that include long-term follow-up are needed to determine the duration of efficacy and the frequency of application.

(...)

The mean amplitude improved in 16 Tds from 2.4 to 5.0 nv/deg2 (p = 0.01) and in 32 Tds from 2.4 to 4.8 nv/deg2 (p = 0.01) in the full-field flicker electroretinography results. Full field flicker electroretinography mean implicit time also improved in 16 Tds from 43.3 to 37.9 ms (p = 0.01).

Huan, L. Clinical manifestation and genetic analysis in Chinese early onset X-linked retinoschisis, 2020

BACKGROUND: X-linked retinoschisis (XLRS) is one type of retinal dystrophy leading to the schisis of the neural retina and causing reduced visual acuity. The study aimed to investigate the clinical manifestations and retinoschisin 1 (RS1) mutations in Chinese patients with early onset XLRS.

METHODS: Thirty-eight probands with early onset XLRS were recruited, comprehensive ophthalmic examination was performed. A targeted gene panel was used to test the RS1 mutations.

RESULTS: All probands had RS1 hemizygous mutations including 16 known and 14 novel mutations. The median onset age was 2 years old (range 0.1–6 years). Probands with onset age ≤1 years. had more complications (retinal detachment and vitreous hemorrhage, $p < 0.001$), more mutations outside the discoidin domain and more non-frameshift mutations than probands with onset age >1 years. Macular and peripheral involvement was present in 77.27% of probands, and inner and outer nuclear layer splitting were present in 53.57% of probands. Electroretinography showed an electronegative waveform. The relatively rare phenotypes of lamellar macular hole and macular hole were present in a unilateral eye in three probands.

CONCLUSION: In conclusion, the early onset XLRS developed more severe complications which need close monitoring and clinical manifestations illustrated here may facilitate the early diagnosis of retinoschisis.

Haseoka T et al. Usefulness of Handheld Electroretinogram System for Diagnosing Blue-Cone Monochromatism in Children, 2020

PURPOSE: To report the diagnosis of three childhood patients with blue-cone monochromatism (BCM) using S-cone electroretinograms (ERG) recorded with RETeval® Complete.

METHODS: We examined three boys initially suspected of having rod monochromatism. S-cone ERG was performed with red background and blue flashed light stimulation using two different intensities: 0.25 cd × s/m2 and 1 cd × s/m2.

RESULTS: Case 1 was a 12-year-old boy with a visual acuity of 0.1 OU. Case 2 was an 8-year-old boy with a visual acuity of 0.3 OD and 0.2 OS. Both cases showed a myopic fundus and nystagmus without any other ocular abnormalities. Case 3 was a 6-year-old boy with a visual acuity of 0.3 OD and 0.4 OS. He also showed myopic fundus changes, but nystagmus was not observed. Rod and maximal responses recorded with RETeval® were likely to be within normal range; however, cone responses were absent in all cases. S-cone ERGs showed positive responses at 40 ms with 0.25 cd × s/m2 intensity in Case 2, and at approximately 30–40 ms with 1.0 cd × s/m2 intensity in all three cases. These ERG findings led to a diagnosis of BCM.

CONCLUSIONS: S-cone ERG of RETeval® was helpful in diagnosing with minimal invasion BCM in childhood patients.

Nadeem, R. Mutations in CERKL and RP1 cause retinitis pigmentosa in Pakistani families, 2020

This study was conducted to identify the genetic basis of retinal dystrophies in consanguineous Pakistani families. We recruited two families with retinitis pigmentosa (RP) displaying visual difficulties, including nyctalopia and constricted visual fields. Linkage analysis and Sanger sequencing resulted in the identification of a previously reported nonsense mutation, c.847C > T, in exon 5 of CERKL in one family and a novel four-base pair deletion in exon 4 of RP1, c.delAGAA4218_4221, leading to premature protein termination in the second family. Here, we report two RP-causing mutations extending the genetic heterogeneity of the disease.

Marmoy, R. An alternative electroretinography protocol for children: a study of diagnostic agreement and accuracy relative to ISCEV standard electroretinograms, 2021

PURPOSE: To assess the diagnostic accuracy and agreement between a paediatric electroretinography protocol used at Great Ormond Street Hospital (GOSH-ERG) and the 'gold standard' international protocol (ISCEV-ERG) in health and disease.

METHODS: Patient databases between 2010 and 2020 were screened to identify children with an ISCEV-ERG recorded within four years of a GOSH-ERG. Electroretinogram (ERG) component peak times and amplitudes were re-measured, and data were analysed in terms of absolute abnormality and proportional deviation from respective reference ranges. Abnormality was defined by the retinal system affected and by individual ERG a- and b-wave component analysis.

RESULTS: A total of 59 patients were included: 38 patients had retinal disease defined by an abnormal ISCEV-ERG and 21 had normal ISCEV-ERGs. When absolute abnormality was defined by combined retinal systems, the GOSH-

ERG showed an excellent overall sensitivity of 95% (accuracy 86%). Individual retinal systems showed good–excellent sensitivity (67%–100%) and specificity (68%–97%). Electroretinogram (ERG) component sensitivities ranged between 60% and 97% and specificities between 79% and 97% dependent upon the protocol step. The proportional relationship appeared mostly linear between protocols. Electroretinogram (ERG) morphology was comparable for both protocols in a range of retinal diseases including those with pathognomonic ERGs.

CONCLUSION: We demonstrate the high diagnostic accuracy of a paediatric ERG protocol (GOSH-ERG) relative to ISCEV standard ERGs. The close proportional deviation and similar waveform morphology indicate ERGs from each protocol are similarly affected in disease. This encourages the use of the GOSH-ERG protocol in the screening, diagnosis and monitoring of retinal disease in children who are unable to comply with the rigorous ISCEV-ERG protocol.

Jin, S. TUBB3 M323V Syndrome Presents with Infantile Nystagmus, 2021

Variants in the TUBB3 gene, one of the tubulin-encoding genes, are known to cause congenital fibrosis of the extraocular muscles type 3 and/or malformations of cortical development. Herein, we report a case of a 6-month-old infant with c.967A>G:p.(M323V) variant in the TUBB3 gene, who had only infantile nystagmus without other ophthalmological abnormalities. Subsequent brain magnetic resonance imaging (MRI) revealed cortical dysplasia. Neurological examinations did not reveal gross or fine motor delay, which are inconsistent with the clinical characteristics of patients with the M323V syndrome reported so far. A protein modeling showed that the M323V mutation in the TUBB3 gene interferes with αβ heterodimer formation with the TUBA1A gene. This report emphasizes the importance of considering TUBB3 and TUBA1A tubulinopathy in infantile nystagmus. A brain MRI should also be considered for these patients, although in the absence of other neurologic signs or symptoms.

Lachmann, E. Isolated juvenile macular dystrophy without posterior column ataxia associated with FLVCR1 mutation, 2021

In this report, we describe a novel clinical phenotype of FLVCR1-associated retinal degeneration without evidence of neurologic involvement due to a compound heterozygous FLVCR1 mutation in a 10-year-old boy.
Typical and atypical retinitis pigmentosa with and without cystoid macular edema have been described in the literature (8,9). The herein described case revealed no peripheral retinal abnormalities in autofluorescence imaging or on scotopic electroretinogram (ERG), yet a profound bilateral macular dystrophy with degeneration of outer retinal layers in OCT imaging (Figure 1e,f), leading to progressive visual deterioration.

Thompson, D. An ERG and OCT study of neuronal ceroid lipofuscinosis CLN2 Battens retinopathy, 2021

BACKGROUND: Late infantile neuronal ceroid lipofuscinosis (CLN2 Batten disease) is a rare, progressive neurodegenerative disease of childhood. The natural history of motor and language regression is used to monitor the efficacy of CNS treatments. Less is known about CLN2 retinopathy. Our aim is to elaborate the nature, age of onset, and symmetry of CLN2 retinopathy using visual electrophysiology and ophthalmic imaging.

SUBJECTS AND METHODS: We reviewed 22 patients with genetically confirmed CLN2 disease; seventeen showing classical and five atypical disease. Flash electroretinograms (ERGs), flash and pattern reversal visual evoked potentials (VEPs), recorded from awake children were collated. Available fundus images were graded, optical coherence tomography (OCT) central subfoveal thickness (CST) measured, and genotype, age, clinical vision assessment and motor language grades assembled.

RESULTS: ERGs show cone/rod system dysfunction preceded by localised macular ellipsoid zone disruption on OCT from 4.8 years. Electroencephalogram (EEG) time-locked spikes confounded both pattern 6/17 (35%) and flash VEPs 12/16 (75%). Paired right eye (RE) and left eye (LE) ERG amplitudes did not differ significantly for each flash stimulus at the p 0.001 level, Wilcoxon ranked signed test. Cone ERGs show a functional deficit before CST thinning in classical disease. Optomap hyper fundus autofluorescence (FAF) at the fovea was noted in three patients with normal ERGs. The oldest patient showed an ovoid aggregate above the external limiting membrane at the fovea, which did not affect the PERG.

CONCLUSION: ERG findings in CLN2 retinopathy show symmetrical cone-rod dysfunction, from 4y10m in this series, but a broad range of ages when ERG function is preserved.

Li, S. Knobloch Syndrome Associated with Novel COL18A1 Variants in Chinese Population, 2021

Knobloch syndrome is an inherited disorder characterized by high myopia, retinal detachment, and occipital defects. Disease-causing mutations have been identified in the COL18A1 gene. This study aimed to investigate novel variants of COL18A1 in Knobloch syndrome and describe the associated phenotypes in Chinese patients. We reported six

patients with Knobloch syndrome from four unrelated families in whom we identified five novel COL18A1 mutations. Clinical examination showed that all probands presented with high myopia, chorioretinal atrophy, and macular defects; one exhibited rhegmatogenous retinal detachment in one eye. Occipital defects were detected in one patient.

Perche O, Electroretinography and contrast sensitivity, complementary translational biomarkers of sensory deficits in the visual system of individuals with fragile X syndrome, 2021

BACKGROUND: Disturbances in sensory function are an important clinical feature of neurodevelopmental disorders such as fragile X syndrome (FXS). Evidence also directly connects sensory abnormalities with the clinical expression of behavioral impairments in individuals with FXS; thus, positioning sensory function as a potential clinical target for the development of new therapeutics. Using electroretinography (ERG) and contrast sensitivity (CS), we previously reported the presence of sensory deficits in the visual system of the Fmr1−/y genetic mouse model of FXS. The goals of the current study were two-folds: (1) to assess the feasibility of measuring ERG and CS as a biomarker of sensory deficits in individuals with FXS, and (2) to investigate whether the deficits revealed by ERG and CS in Fmr1−/y mice translate to humans with FXS.

METHODS: Both ERG and CS were measured in a cohort of male individuals with FXS (n = 20, 18–45 years) and agematched healthy controls (n = 20, 18–45 years). Under light-adapted conditions, and using both single flash and flicker (repeated train of flashes) stimulation protocols, retinal function was recorded from individual subjects using a portable, handheld, full-field flash ERG device (RETeval®, LKC Technologies Inc., Gaithersburg, MD, USA). CS was assessed in each subject using the LEA SYMBOLS® low-contrast test (Good-Lite, Elgin, IL, USA).

RESULTS: Data recording was successfully completed for ERG and assessment of CS in most individuals from both cohorts demonstrating the feasibility of these methods for use in the FXS population. Similar to previously reported findings from the Fmr1−/y genetic mouse model, individuals with FXS were found to exhibit reduced b-wave and flicker amplitude in ERG and an impaired ability to discriminate contrasts compared to healthy controls.

Waldie, A. Electrophysiological Assessment in Birdshot Chorioretinopathy: Flicker Electroretinograms Recorded with a Handheld Device, 2022

BACKGROUND: The flicker electroretinogram (ERG) is a sensitive indicator of retinal dysfunction in birdshot chorioretinopathy (BCR). We explored recordings from a handheld device in BCR, comparing these with conventional recordings in the same patients and with handheld ERGs from healthy individuals.

METHODS: Non-mydriatic flicker ERGs, using the handheld RETeval system (LKC Technologies), were recorded with skin electrodes at two centers. At one center (group 1), the stimuli (85 Td·s, 850 Td background) delivered retinal illuminance equivalent to international standards; at the other center (group 2), a different protocol was used (32 Td·s, no background). Patients also underwent international standard flicker ERG recordings with conventional electrodes following mydriasis. Portable ERGs from patients were also compared with those from healthy individuals.

RESULTS: Thirty-two patients with BCR (mean age ± SD, 56.4 ± 11.3 years) underwent recordings. Portable and standard ERG parameters correlated strongly ($r > 0.75$, $P < 0.01$) in both groups. Limits of agreement for peak times were tighter in group 1 (n = 21; −4.3 to +2.0 ms [right eyes], −3.9 to 1.5 ms [left eyes]) than in group 2 (n = 11; −3.4 to +6.9 ms [right eyes], −4.8 to +9.0 ms [left eyes]). Compared with healthy controls (n = 66 and n = 90 for groups 1 and 2, respectively), patients with BCR showed smaller mean amplitudes and longer peak times.

CONCLUSION: Portable ERGs correlated strongly with conventional recordings, suggesting potential in rapid assessment of cone system function in office settings.

TRANSLATIONAL RELEVANCE: Flicker ERGs, known to be useful in BCR, can be obtained rapidly with a portable device with skin electrodes and natural pupils.

Moon, D. Precision Medicine through Next-Generation Sequencing in Inherited Eye Diseases in a Korean Cohort, 2022

In this study, we investigated medically or surgically actionable genes in inherited eye disease, based on clinical phenotype and genomic data. This retrospective consecutive case series included 149 patients with inherited eye diseases, seen by a single pediatric ophthalmologist, who underwent genetic testing between 1 March 2017 and 28 February 2018. Variants were detected using a target enrichment panel of 429 genes and known deep intronic variants associated with inherited eye disease. Among 149 patients, 38 (25.5%) had a family history, and this cohort includes heterogeneous phenotype including anterior segment dysgenesis, congenital cataract, infantile nystagmus syndrome, optic atrophy, and retinal dystrophy. Overall, 90 patients (60.4%) received a definite molecular diagnosis. Overall, NGS-guided precision care was provided to 8 patients (5.4%). The precision care included cryotherapy to prevent retinal detachment in COL2A1 Stickler syndrome, osteoporosis management in patients with LRP5-

associated familial exudative vitreoretinopathy, and avoidance of unnecessary phlebotomy in hyperferritinemia-cataract syndrome. A revision of the initial clinical diagnosis was made in 22 patients (14.8%). Unexpected multi-gene deletions and dual diagnosis were noted in 4 patients (2.7%). We found that precision medical or surgical managements were provided for 8 of 149 patients (5.4%), and multiple locus variants were found in 2.7% of cases. These findings are important because individualized management of inherited eye diseases can be achieved through genetic testing.

Nasser et al. Ophthalmic and Genetic Features of Bardet Biedl Syndrome in a German Cohort, 2022

The aim of this study was to characterize the ophthalmic and genetic features of Bardet Biedl (BBS) syndrome in a cohort of patients from a German specialized ophthalmic care center. Sixty-one patients, aged 5–56 years, underwent a detailed ophthalmic examination including visual acuity and color vision testing, electroretinography (ERG), visually evoked potential recording (VEP), fundus examination, and spectral domain optical coherence tomography (SD-OCT). Adaptive optics flood illumination ophthalmoscopy was performed in five patients. All patients had received diagnostic genetic testing and were selected upon the presence of apparent biallelic variants in known BBSassociated genes. All patients had retinal dystrophy with morphologic changes of the retina. Visual acuity decreased from ~0.2 (decimal) at age 5 to blindness 0 at 50 years. Visual field examination could be performed in only half of the patients and showed a concentric constriction with remaining islands of function in the periphery. ERG recordings were mostly extinguished whereas VEP recordings were reduced in about half of the patients. The cohort of patients showed 51 different likely biallelic mutations—of which 11 are novel—in 12 different BBS-associated genes. The most common associated genes were BBS10 (32.8%) and BBS1 (24.6%), and by far the most commonly observed variants were BBS10 c.271dup;p.C91Lfs*5 (21 alleles) and BBS1 c.1169T>G;p.M390R (18 alleles). The phenotype associated with the different BBS-associated genes and genotypes in our cohort is heterogeneous, with diverse features without genotype–phenotype correlation. The results confirm and expand our knowledge of this rare disease.

Sobolewska, M. CDHR1-Related Cone–Rod Dystrophy: Clinical Characteristics, Imaging Findings, and Genetic Test Results—A Case Report, 2023

BACKGROUND: Cone–rod dystrophies (CRDs) are a heterogeneous group of inherited retinal diseases (IRDs) characterized by cone photoreceptor loss, that is followed by subsequent rod photoreceptor impairment.

CASE PRESENTATION: A 49-year-old man complaining of diminution of vision in both eyes (OU) was referred to our outpatient clinic. He reported visual loss for 5 years, but it was most progressive during the last few months. The best-corrected visual acuity (BCVA) at presentation was 0.4 in the right eye (RE) and 1.0 in the left eye (LE). Fundus fluorescein angiography (FFA) revealed granular hyperfluorescence in the macula and concomitant areas of capillary atrophy. Flash full-field electroretinography (ffERG) showed lowering of a and b waves as well as prolonged peak time in light-adapted conditions. However, outcomes of dark-adapted ERGs were within normal limits. Based on the constellation of clinical, angiographic, and electrophysiological tests findings, a diagnosis of IRD was suspected. Genetic testing showed a homozygous, pathogenic c.783G>A mutation in the cadherin-related family member 1 (CDHR1) gene, which confirmed CRD type 15 (CRD15).

CONCLUSIONS: We demonstrate the clinical characteristics, retinal imaging outcomes, and genetic test results of a patient with CRD15. Our case contributes to expanding our knowledge of the clinical involvement of the pathogenic mutation c.783G>A in CDHR1 variants.

Albuquerque, ML. ERG and OCT abnormalities in retinoblastoma after melphalan intravitreous injection, 2021

The authors report full-field electroretinogram and optical coherence tomography findings of intravitreal melphalan retinal toxicity. An 18-month-old girl with unilateral group D retinoblastoma was evaluated with light-adapted 3 full-field electroretinogram protocol and optical coherence tomography (I-Stand optical coherence tomography, Optovue) after treatment with intravitreal melphalan for active vitreous seeds. After the third injection, the child developed retinal pigment epithelial changes near the injection site. The photopic response of the full-field electroretinogram standard flash cones showed a decrease in amplitude responses of waves a and b in the affected eye compared to the contralateral eye. Optical coherence tomography showed loss of photoreceptors and outer nuclear layers in the affected eye. Melphalan toxicity is dose-dependent, and despite its treatment benefits, it can affect vision. Our case shows an updated, in-depth retinal toxicity assessment of intravitreal melphalan in the human retina with optical coherence tomography and its correlation with electroretinogram changes.

Gonzalez, GM. Musculoskeletal Manifestations in Patients with Bardet-Biedl Syndrome: A Report of Two Cases, 2023

We report two patients with musculoskeletal manifestations as part of the Bardet-Biedl syndrome. The first patient (case 1) was born with polydactyly and later diagnosed with coxa vara. He had homozygous pathogenic mutation in the BBS1 gene of the variant c.1645G>T (p.Glu459*). The second patient (case 2) had nyctalopia and progressive vision worsening had osteoarthritis symptoms. He had a heterozygous mutation in the BBS1 gene of the variant c.1169T>G (p.Met390Arg). Although polydactyly is the most prevalent musculoskeletal association in patients with the syndrome, co-management of the musculoskeletal manifestations remains of utmost importance in patients with the syndrome.

Sather, R. Septo-optic dysplasia presenting with nystagmus, pseudo-disc edema, and fovea hypoplasia, 2022

BACKGROUND: Septo-optic dysplasia (SOD) is a condition that affects the early development of the brain and eyes. It presents with a combination of optic nerve hypoplasia, brain midline structure abnormalities, and pituitary gland hypoplasia.

METHODS: This is a case report of a 4-year-old male who presented with low amplitude horizontal nystagmus and decreased visual acuity 20/60 OU. Further imaging and electrophysiology were conducted to classify the ocular presentation.

RESULTS: No iris transillumination was noted, but foveal hypoplasia and disc edema were evident on fundus examination. This prompted neurology consultation and MRI imaging. The MRI was consistent with the diagnosis of SOD showing hypoplasia of the optic nerves, chiasm, and tracts and an absent septum pellucidum, but with normal pituitary development and function. Lumbar puncture and intracranial pressure were normal. Genetic testing identified one pathogenic variant in the SLC45A2, indicating carrier status for oculocutaneous albinism type 4 (OCA4). Flash Visual Evoked Potentials (VEPs) were consistent with chiasm dysfunction or hypoplasia rather than the chiasmal misrouting of OCA.

CONCLUSION: This case report further elaborates the phenotypic variation of SOD, with the finding of blurred disc margins, in the absence of the typical optic nerve double ring sign and with normal intracranial pressure. The findings of fovea hypoplasia and blond fundi lead to the suspicion of OCA either as a separate diagnosis with a second pathogenic variant in SCL45A2 not yet identified or in association with SOD. This case highlights the importance of electrophysiology to help distinguish chiasmal hypoplasia or dysfunction from OCA misrouting.

Mizumoto, K. A Japanese boy with Bardet-Biedl syndrome caused by a novel homozygous variant in the ARL6 gene who was initially diagnosed with retinitis punctata albescens, 2022

PURPOSE: Bardet-Biedl Syndrome (BBS) is an autosomal recessive systemic disorder characterized by retinitis pigmentosa, polydactyly, obesity, intellectual disability, renal impairments, and hypogonadism. The purpose of this study was to determine the ocular characteristics of a boy with BBS caused by a novel homozygous variant in the ARL6 (alternative named BBS3) gene who had been originally diagnosed with retinitis punctata albescens.

METHODS: This was an observational case study. The patient underwent ophthalmological examinations, electroretinography, and genetic analyses using whole-exome sequencing.

RESULTS: A 7-year-old boy was examined in our hospital with complaints of a progressive reduction of his visual acuity and night blindness in both eyes. There was no family history of eye diseases and no consanguineous marriage. Fundus examinations showed numerous white spots in the deep retina and retinal pigment epithelium. Fundus autofluorescence showed hypofluorescence consistent with these spots. Both the scotopic and photopic components of the full-field electroretinographies were non-detectable. Based on these clinical findings, this boy was suspected to have retinitis punctata albescens. Subsequent genetic testing using whole-exome sequencing revealed a novel homozygous variants in the ARL6/BBS3 gene (NM_001278293.3:c.528G>A, (p.Trp176Ter)). A systemic examination by the pediatric department revealed that this boy had a history of a surgical excision of polydactyly on his left foot when he was born, and that he was mildly obese. There were no prominent intellectual or gonadal dysfunctions, no craniofacial or dental abnormalities, no congenital heart disease, and no hearing impairment. He was then clinically and genetically diagnosed with BBS.

CONCLUSION and importance: In children with night blindness and progressive visual dysfunction, it is important for ophthalmologists to consult clinical geneticists and pediatricians to rule out the possibility of systemic diseases such as BBS.

Wang, Y. Ocular findings and genetic test in Alström syndrome in childhood, 2022

This study aimed to investigate the mutation spectrums and ocular features of Alstr¨ om syndrome (AS) patients. Six AS patients from five unrelated families were included. Ocular and systemic examinations were performed in all subjects. Whole-exome sequencing (WES) was performed in the probands, and Sanger sequencing was performed for mutation validation and segregation analysis. Among the six patients, the first symptoms included nystagmus, poor fixation, and photophobia. Five patients had high hyperopia, four of whom (80%) were initially diagnosed with amblyopia before referral with prescribed corrective lenses and amblyopia treatment, but no improvement was obtained. Optical coherence tomography (OCT) revealed progressive damage to the photo receptor layer, including blurred ellipsoid zone (EZ) and lack of interdigitation zone (IZ) within the macula, and thorough loss of photoreceptor layer in the peripheral retina. Electroretinograms (ERG) demonstrated severely diminished cone and rod responses. WES identified biallelic variants of ALMS1 in all the six patients, including two novels, c.3892C > T (p.Gln1298*) and c.2888_2897del (p.Ser963Thrfs*15) and five knowns, c.10819C > T (p.Arg3607Trp), c.2090C > A (p.Ser697*), c.4891C > T (p.Gln1631*), c.10825C > T (p.Arg3069*) and c.6430C > T (Arg2146*). In conclusion, this study expanded the ocular features and genotypic spectrum of AS. High hyperopia is a significant and common feature of AS. OCT and ERG are essential accessory techniques for the diagnosis of AS. If a patient had high hyperopia with a noneffective response to amblyopic treatment, the diagnosis of AS should be suspected, and detailed ocular examination, systemic evaluation, and genetic testing recommended.

Wei, x. Leber congenital amaurosis as the initial and essential manifestation in a Chinese patient with autoimmune polyglandular syndrome Type 1, 2023

PURPOSE: Autoimmune polyglandular syndrome Type 1 (APS-1) is a rare autosomal recessive disorder caused by defects in the autoimmune regulator (AIRE) gene. Patients are generally diagnosed at ages between five and fifteen years when they exhibit three or more manifestations, most typically mucocutaneous candidiasis, autoimmune Addison's disease, and hypoparathyroidism. Our study aims to report the first case of a Chinese APS-1 patient, presented with LCA as the initial and essential clinical feature of this rare syndrome.

METHODS: Detailed medical and family history were recorded for the patient. Also, the comprehensive ophthalmological examinations were conducted. Whole exome sequencing (WES) was applied to screen pathogenic variants. Sanger sequencing validation and segregation analysis were further performed for confirmation.

RESULTS: A 3-year-old boy with severely impaired vision and initially referred as LCA. However, with a detailed history review, oral candidiasis, dental enamel hypoplasia, and nail candida infection were revealed. Moreover, genetic analysis revealed the homozygous c.769C>T (p.R257X) in AIRE gene (NM_000383.3) as the causative variant.

CONCLUSION: We presented one case diagnosed with APS-1 based on clinical characteristics and genetic analysis. Our study demonstrated that LCA could serve as a warning sign for APS-1 and a potential trigger of early screening, which might prevent life-threatening complications.

Li, X, R. Double Hyperautofluorescence Rings as a Sign of CFAP410-related Retinopathy, 2023

BACKGROUND: Variants in CFAP410 have been reported to cause retinal dystrophy with or without systemic symptoms. This study was designed to characterize the fundus changes of patients with biallelic variants in CFAP410.

METHODS: Variants in CFAP410 were identified through whole exome sequencing and targeted exome sequencing of 10,530 probands. Biallelic variants in CFAP410 were evaluated by comprehensive in silico analysis and confirmed by Sanger sequencing and segregation analysis. Ocular phenotypes including fundus photographs, scanning laser ophthalmoscopy, autofluorescence images, ERG, and optical coherence tomography were characterized.

RESULTS: Nine patients from eight families were homozygotes or compound heterozygotes for a total of four variants in CFAP410, including c.144-6_159del (novel), c.340_351dup, c.347C>T, and c.545+1G>A. Three patients were diagnosed with cone–rod dystrophy, and the remaining six patients with RP. Among eight patients performed with ultra-wide scanning laser ophthalmoscopy, double hyperautofluorescence rings inside and outside of the macular vascular arcades were observed in six patients, and the remaining two older patients demonstrated single hyperautofluorescence ring surrounded by pigmentation. CFAP410-associated retinopathy in early stage was generally tapetoretinal degeneration without noticeable bone spicule pigmentation, with more severe degeneration in the inferior nasal retina. ERG recordings delineated a severely reduced cone response and mildly to severely reduced rod response. Posterior staphyloma was seen in seven patients who underwent optical coherence tomography examinations.

CONCLUSION: The present study demonstrates the fundus characteristics of patients with biallelic variants in CFAP410 and expands the genotype–phenotype spectrum of CFAP410-related retinal degeneration, in which posterior staphyloma together with double hyperautofluorescence rings might be common peculiar signs.

Constable, P. Suspected case of benign familial fleck retina with functional loss, 2023

Inherited retinal dystrophies typically affect vision in early childhood; however, this case highlights a late onset retinal dystrophy presenting in midlife and the need for extended visual electrophysiology testing to determine the etiology.

A 53-year-old female was referred for visual electrophysiology following a routine optometric eye examination in which yellow flecks were noted in both fundi and the patient had reported a recent near accident whilst driving at night. There was no reported family history of eye disease. Retinal examination identified bilateral yellow punctate and irregularly shaped lesions throughout the posterior poles sparing the macula region. Fundus autofluorescence showed coinciding hyperfluorescence with the lesions and bilateral hypofluorescent crescents superior to the macular with corresponding retinal thinning. Visual fields and color vision were normal. ISCEV standard 20 min and extended 60-min dark adapted electroretinograms were recorded. Recovery to normal b-wave amplitudes was noted in the DA0.01 flash but reduced a-wave amplitudes were noted in the DA3 and DA10 flash following both dark adapted periods. Cone function was reduced but within normal limits. Genetic screening revealed a previously unreported variant of unknown significance in the gene PLA2G5:c.40 + 5del (rs1364254561) which is a member of the phospholipase A2 family and is associated with familial benign flecked retina.

Siddharth, S. Multimodal analysis of two siblings with Oguchi disease, 2024

A 9-year-old female patient presented with complaints of diminution of vision at night since early childhood. She had a best corrected visual acuity (BCVA) of 6/12, N6 with normal intraocular pressure (IOP). The anterior segment examination was unremarkable. However, on evaluating the fundus, a golden-yellow sheen was visible throughout the retina. A high definition radial optical coherence tomography (HD radial OCT) (Cirrus HD-OCT 5000, Carl Zeiss Meditec, Inc., USA) [Fig. 3a and b] and a macular cube OCT revealed normal foveal contour and no significant changes at the macula. Fundus photos (TRC-50DX, Topcon, Inc., Japan) were taken before [Fig. 1a and b] and after [Fig. 1c and d] 20 minutes of dark adaptation, which were in concurrence with the Mizuo–Nakamura phenomenon, and a full field electroretinogram (ERG) (RETeval, LKC Technologies, Inc., USA) [Fig. 4] with light adaptation followed by 20 minutes of dark adaptation was recorded. ERG revealed decreased a wave and b wave amplitudes in both scotopic and photopic conditions.

Sather, R. The Clinical Findings, Pathogenic Variants, and Gene Therapy Qualifications Found in a Leber Congenital Amaurosis Phenotypic Spectrum Patient Cohort, 2024

This retrospective study examines the clinical characteristics and underlying genetic variants that exist in a Leber congenital amaurosis (LCA) patient cohort evaluated at the inherited retinal disease (IRD) clinic at the University of Minnesota (UMN)/M Health System. Our LCA cohort consisted of 33 non-syndromic patients and one patient with Joubert syndrome. We report their relevant history, clinical findings, and genetic testing results. We monitored disease presentation utilizing ocular coherence tomography (OCT) and fundus autofluorescence (FAF). Electroretinogram testing (ERG) was performed in patients when clinically indicated. Next-generation sequencing (NGS) and genetic counseling was offered to all evaluated patients. Advanced photoreceptor loss was noted in 85.7% of the subjects. All patients who underwent FAF had findings of either a ring of macular hypo/hyper AF or peripheral hypo-AF. All patients had abnormal ERG findings. A diagnostic genetic test result was identified in 74.2% of the patients via NGS single-gene testing or panel testing. Two patients in our cohort qualified for Luxturna® and both received treatment at the time of this study. These data will help IRD specialists to understand the genetic variants and clinical presentations that characterize our patient population in the Midwest region of the United States.

Jin, Y. Genotype-Phenotype of CRB1-Associated Early-Onset Retinal Dystrophy: Novel Insights on Retinal Architecture and Therapeutic Window for Clinical Trials, 2024

OBJECTIVE: The purpose of this study was to investigate the genotypic and phenotypic characteristics of CRB1-associated early onset retinal dystrophy (CRB1-eoRD) and retinal architecture by swept-source optical coherence tomography (SS-OCT).

METHODS: Eleven probands with CRB1-eoRD were recruited. Clinical information, genetic analysis, and comprehensive ophthalmic examinations including SS-OCT and SS-OCT angiography (SS-OCTA) were conducted.

RESULTS: A total of 81.8% (9/11) of CRB1-eoRD presented as Leber congenital amaurosis (LCA). Common clinical manifestations included coin-like yellow-white retinal spots (20/22, 90.9%) and para-arteriolar retinal pigment

epithelial retention (12/22, 54.5%). Nineteen different CRB1 variants were detected in our case series, including 12 missense, 3 frameshifts, 3 nonsense, and 1 splicing. Of them, 12 variants had been reported, and 7 were novel. SS-OCT showed thinner central macula (the LCA group, P < 0.0001), thicker total retina (P < 0.0001), thinner outer retina (P < 0.05), and thicker inner retina (P < 0.0001) compared with the healthy control. The inner/outer (I/O) retina thickness ratio of CRB1-eoRD was 3.0, higher than the healthy control of 1.2 and other inherited retinal diseases (IRDs) of 2.2 (P < 0.0001 and P = 0.0027, respectively). SS-OCTA revealed an increased vascular density and perfusion area of the superficial vascular complex and deep vascular complex in CRB1-eoRD.

CONCLUSION: LCA emerges as a frequently occurring phenotype in CRB1-eoRD. The unique features of SS-OCT and SS-OCTA are illustrated, and the novel biomarker, I/O ratio, may facilitate early diagnosis. The insights gained from this study hold significant value in determining the treatment window for potential forthcoming CRB1 gene therapy.

Suga, A. A homozygous structural variant of RPGRIP1 is frequently associated with achromatopsia in Japanese patients with IRD, 2024

OBJECTIVE: Achromatopsia (ACHM) is an early-onset cone dysfunction caused by five genes with cone-specific functions (CNGA3, CNGB3, GNAT2, PDE6C, and PDE6H), and by ATF6, a transcription factor with ubiquitous expression. To improve the relatively low variant detection ratio in these genes in a cohort of exome-sequenced Japanese patients with inherited retinal diseases (IRD), we performed genome sequencing to detect structural variants and intronic variants in patients with ACHM.

METHODS: Genome sequencing of 10 ACHM pedigrees was performed after exome sequencing. Structural, non-coding, and coding variants were filtered based on segregation between the affected and unaffected in each pedigree. Variant frequency and predicted damage scores were considered in identifying pathogenic variants..

RESULTS: A homozygous deletion involving exon 18 of RPGRIP1 was detected in 5 of 10 ACHM probands, and variant inheritance from each parent was confirmed. This deletion was relatively frequent (MAF = 0.0023) in the Japanese population but was only homozygous in patients with ACHM among the 199 Japanese IRD probands analyzed by the same genome sequencing pipeline.

CONCLUSION: The deletion involving exon 18 of RPGRIP1 is a prevalent cause of ACHM in Japanese patients and contributes to the wide spectrum of RPGRIP1associated IRD phenotypes, from Leber congenital amaurosis to ACHM.

Nagarajan, S. Electroretinogram as a Screening Tool to Assess Vigabatrin-Induced Retinal Toxicity in Children With Infantile Spasms, 2024

PURPOSE: To assess the utility of electroretinogram (ERG) as a screening tool for vigabatrin-induced retinal toxicity in children with infantile spasms.

METHODS: This was an observational cohort study including children with infantile spasms receiving treatment with vigabatrin. A 30-Hz flicker potential ERG, using the RETeval system (LKC Technologies), was done at baseline before starting vigabatrin at 6 months and 1 year. The amplitudes were recorded.

RESULTS: Eleven children were included in the study. The most common etiologic factor for infantile spasms was tuberous sclerosis (36.4%) followed by West syndrome (27.3%). The mean age of the children was 7.14 ± 2.9 months, with a range of 3 to 16 months. The mean difference in amplitude was 3.21 ± 2.45 and 5.72 ± 4.18 μV at 6 and 12 months follow-up, respectively (P < .001). Eight of the 11 children (72.7%) showed vigabatrin-induced retinal toxicity, and all 8 children were receiving vigabatrin for more than 6 months.

CONCLUSIONS: ERG can be used for vigabatrin-induced retinal toxicity monitoring in children with infantile spasms. Vigabatrin-induced retinal toxicity is related to the duration of treatment rather than cumulative dosage.

Wei, X. Leber congenital amaurosis as the initial and essential manifestation in a Chinese patient with autoimmune polyglandular syndrome Type 1, 2024

PURPOSE: Autoimmune polyglandular syndrome Type 1 (APS-1) is a rare autosomal recessive disorder caused by defects in the autoimmune regulator (AIRE) gene. Patients are generally diagnosed at ages between five and fifteen years when they exhibit three or more manifestations, most typically mucocutaneous candidiasis, autoimmune Addison's disease, and hypoparathyroidism. Our study aims to report the first case of a Chinese APS-1 patient, presented with LCA as the initial and essential clinical feature of this rare syndrome.

METHODS: Detailed medical and family history were recorded for the patient. Also, the comprehensive ophthalmological examinations were conducted. Whole exome sequencing (WES) was applied to screen pathogenic variants. Sanger sequencing validation and segregation analysis were further performed for confirmation.

RESULTS: A 3-year-old boy with severely impaired vision and initially referred as LCA. However, with a detailed history review, oral candidiasis, dental enamel hypoplasia, and nail candida infection were revealed. Moreover, genetic analysis revealed the homozygous c.769C>T (p.R257X) in AIRE gene (NM_000383.3) as the causative variant.

CONCLUSIONS: We presented one case diagnosed with APS-1 based on clinical characteristics and genetic analysis. Our study demonstrated that LCA could serve as a warning sign for APS-1 and a potential trigger of early screening, which might prevent life threatening complications.

Aghazadeh, H. Upward saccadic intrusions as the presenting feature for incomplete congenital stationary night blindness, 2024

We describe the case of a 9-month-old boy presenting with isolated intermittent vertical eye movements most in keeping with upward saccadic pulses, a form of saccadic intrusions. Full-field electroretinogram was consistent with a generalized retinal dystrophy, and genetic testing revealed a hemizygous pathogenic mutation in the CACNA1F gene, confirming the diagnosis of incomplete congenital stationary night blindness (iCSNB). This case describes vertical saccadic pulses as the sole presenting sign of a retinal dystrophy.

Bodenbender, JP. Comprehensive analysis of two hotspot codons in the TUBB4B gene and associated phenotypes, 2024

Our purpose was to elucidate the genotype and ophthalmological and audiological phenotype in TUBB4B-associated inherited retinal dystrophy (IRD) and sensorineural hearing loss (SNHL), and to model the effects of all possible amino acid substitutions at the hotspot codons Arg390 and Arg391. Six patients from five families with heterozygous missense variants in TUBB4B were included in this observational study. Ophthalmological testing included best-corrected visual acuity, fundus examination, optical coherence tomography, fundus autofluorescence imaging, and full-field electroretinography (ERG). Audiological examination included pure-tone and speech audiometry in adult patients and auditory brainstem response testing in a child. Genetic testing was performed by disease gene panel analysis based on genome sequencing. The molecular consequences of the substitutions of residues 390 and 391 on TUBB4B and its interaction with α-tubulin were predicted in silico on its three-dimensional structure obtained by homology modelling. Two independent patients had amino acid exchanges at position 391 (p.(Arg391His) or p.(Arg391Cys)) of the TUBB4B protein. Both had a distinct IRD phenotype with peripheral round yellowish lesions with pigmented spots and mild or moderate SNHL, respectively.Yet the phenotype was milder with a sectorial pattern of bone spicules in one patient, likely due to a genetically confirmed mosaicism for p.(Arg391His). Three patients were heterozygous for an amino acid exchange at position 390 (p.(Arg390Gln) or p.(Arg390Trp)) and presented with another distinct retinal phenotype with well demarcated pericentral retinitis pigmentosa. All showed SNHL ranging from mild to severe. One additional patient showed a variant distinct from codon 390 or 391 (p.(Tyr310His)), and presented with congenital profound hearing loss and reduced responses in ERG. Variants at codon positions 390 and 391 were predicted to decrease the structural stability of TUBB4B and its complex with α-tubulin, as well as the complex affinity. In conclusion, the twofold larger reduction in heterodimer affinity exhibited by Arg391 substitutions suggested an association with the more severe retinal phenotype, compared to the substitution at Arg390.

Merle, D. Diagnosis of Incomplete Congenital Stationary Night Blindness in a 2-year-old boy, 2024

Congenital stationary night blindness (CSNB) is an umbrella term for a clinically and genetically heterogeneous group of rare inherited retinal diseases (IRDs). Incomplete CSNB (iCSNB) is a rare subtype, with only around 30 detailed clinical case descriptions (excluding reports on female carriers) published so far [1],[2],[3],[4],[5]. First symptoms such as nyctalopia, nystagmus, strabismus and markedly reduced visual acuity (VA) typically occur within the first year of life, with nystagmus usually being the first observable symptom [6].

Huang, X. De novo variation in ARID1B gene causes Coffin-Siris syndrome 1 in a Chinese family with excessive early-onset high myopia, 2024

Coffin-Siris syndrome (CSS) is a rare autosomal dominant inheritance disorder characterized by distinctive facial features, hypoplasia of the distal phalanx or nail of the fifth and additional digits, developmental or cognitive delay of varying degree, hypotonia, hirsutism/hypertrichosis, sparse scalp hair and varying kind of congenital anomalies. CSS can easily be misdiagnosed as other syndromes or disorders with a similar clinical picture because of their genetic

and phenotypic heterogeneity. We describde the genotype-phenotype correlation of one patient from a healthy Chinese family with a novel genotype underlying CSS, who was first diagnosed in the ophthalmology department as early-onset high myopia (eoHM). Comprehensive ophthalmic tests as well as other systemic examinations were performed on participants to confirm the phenotype. The genotype was identified using whole exome sequencing, and further verified the results among other family members by Sanger sequencing. Real-time quantitative PCR (RT-qPCR) technology was used to detect the relative mRNA expression levels of candidate genes between proband and normal family members. The pathogenicity of the identified variant was determined by The American College of Medical Genetics and Genomics (ACMG) guidelines. STRING protein-protein interactions (PPIs) network analysis was used to detect the interaction of candidate gene-related proteins with high myopia generelated proteins. The patient had excessive eoHM, cone-rod dystrophy, coarse face, excessive hair growth on the face, sparse scalp hair, developmental delay, intellectual disability, moderate hearing loss, dental hypoplasia, patent foramen ovale, chronic non-atrophic gastritis, bilateral renal cysts, cisterna magna, and emotional outbursts with aggression. The genetic assessment revealed that the patient carries a de novo heterozygous frameshift insertion variant in the ARID1B c.3981dup (p.Glu1328ArgfsTer5), which are strongly associated with the typical clinical features of CSS patients. The test results of RT-qPCR showed that mRNA expression of the ARID1B gene in the proband was approximately 30% lower than that of the normal control in the family, suggesting that the variant had an impact on the gene function at the level of mRNA expression. The variant was pathogenic as assessed by ACMG guidelines. Analysis of protein interactions in the STRING online database revealed that the ARID1A protein interacts with the high myopia gene-related proteins FGFR3, ASXL1, ERBB3, and SOX4, whereas the ARID1A protein antagonizes the ARID1B protein. Therefore, in this paper, we are the first to report a de novo heterozygous frameshift insertion variant in the ARID1B gene causing CSS with excessive eoHM. Our study extends the genotypic and phenotypic spectrums for ARID1B-CSS and supplies evidence of significant association of eoHM with variant in ARID1B gene. As CSS has high genetic and phenotypic heterogeneity, our findings highlight the importance of molecular genetic testing and an interdisciplinary clinical diagnostic workup to avoid misdiagnosis as some disorders with similar manifestations of CSS.

Kannan, K. Electroretinographic changes in the inner and outer retinal layers before and after intravenous chemotherapy for retinoblastoma, 2024

PURPOSE: To study the inner and outer retinal functions using a full-field electroretinogram (ERG) before and after intravenous chemotherapy (IVC) in children with retinoblastoma (RB).

METHODS: Of the 11 eyes, seven had RB and four were normal. All children were examined under anesthesia using a handheld ERG machine with a standard protocol – light-adapted single-flash ERG (fERG), photopic single-flash 3.0- and 30-Hz flickers, and photopic negative response (PhNR) amplitudes at 72 ms (P72). The amplitudes and peak times were compared before and after IVC.

RESULTS: Post-chemotherapy tumor regressed in all seven eyes. Of the seven eyes, the fERG peak time (a-wave) was delayed in two eyes (29%), whereas the b-wave was delayed in six eyes (86%). The fERG amplitude height for a- and b-waves decreased in five eyes (71%) and six eyes (86%), respectively. In addition, photopic flicker 30-Hz b-wave peak time delayed in five eyes (71%), whereas the b-wave amplitude height decreased in six eyes (86%). Simultaneously, the P72 amplitude height decreased in six eyes (86%), whereas the P-ratio increased in all seven eyes (100%). In comparison, the ERG responses improved in three of the four contralateral normal eyes. Overall, the cone function improved in two eyes (29%), whereas cone bipolar cell and retinal ganglion cell (RGC) function improved in one eye (14%) each.

CONCLUSION: Comparison of light-adapted ERG changes before and after IVC showed reduced amplitudes and delayed peak times for both a and b waveforms, as well as reduced PhNR amplitude attributable to bipolar and RGC injury.

Choi, Y. Clinical and Genetic Features of Korean Patients with Achromatopsia, 2024

This multicenter study aimed to characterize Korean patients with achromatopsia. The patients' genotypes and phenotypes were retrospectively evaluated. Twenty-one patients (with a mean age at the baseline of 10.9 years) were enrolled and followed up for a mean of 7.3 years. A targeted gene panel or exome sequencing was performed. The pathogenic variants of the four genes and their frequencies were identified. CNGA3 and PDE6C were equally the most prevalent genes: CNGA3 (N = 8, 38.1%), PDE6C (N = 8, 38.1%), CNGB3 (N = 3, 14.3%), and GNAT2 (N = 2, 9.5%). The degree of functional and structural defects varied among the patients. The patients' age exhibited no significant correlation with structural defects. During the follow-up, the visual acuity and retinal thickness did not change significantly. In CNGA3-achromatopsia patients, a proportion of patients with a normal foveal ellipsoid zone on the OCT was significantly higher than that of patients with other causative genes (62.5% vs. 16.7%; p = 0.023). In PDE6C-achromatopsia patients, the same proportion was significantly lower than that of patients with other causative genes (0% vs. 58.3%; p = 0.003). Korean patients with achromatopsia showed similar clinical features but a

higher prevalence of PDE6C variants than those of other ethnic groups. The retinal phenotypes of the PDE6C variants were more likely to be worse than those of other genes.

Loh, L. The impact of using reverse polarity text for children with vision impairment assessed using light-adapted flicker electroretinogram, 2024

CLINICAL RELEVANCE: Children with vision impairment can have difficulty accessing classroom reading material and knowledge of which students are likely to have improved performance reading performance with reverse polarity would be of value to educators.

BACKGROUND: Printed material is typically presented as black text on a white background; however, reversing the polarity to white text on a black background may improve the reading speed for children with vision impairment. This study sought to identify the visual function or pathological features of children with vision impairment where reversing the polarity of text would improve their reading performance.

METHODS: Forty-eight vision-impaired participants (27 male), aged 5–18 years with binocular visual acuities between 0.18–1.52 logMAR, were included. Reading performance was assessed by changes in Critical Print Size (ΔCPS), Maximum Reading Speed (ΔMRS) in normal and reverse polarity digital print, and numeric reading speed (ΔNRS) with normal and reverse polarity fonts. Correlations were made with 30 Hz flicker electroretinogram amplitude and high/low contrast acuity. Paired nonparametric tests evaluated significance in pathological condition groups.

RESULTS: Significant negative correlations were only found between the 30 Hz flicker amplitude and ΔMRS ($r = -.42$, $p = .028$) and ΔNRS ($r = -.46$, $p = .027$). Follow-up pairwise comparisons based on pathology group only showed a significant effect of the retinal dystrophy group and CPS ($n = 12$, $z = -2.24$, $p = .025$). All other pairwise comparisons based on group were non-significant ($p > .05$).

CONCLUSIONS: This study did not identify a specific pathological group or visual functional measure that could be used as a clinical marker to predict the impact of reversing polarity. However, significant improvements could be made in reading performance for some children and so a reading performance assessment is recommended for all children with vision impairment.

Surl, D. Clinician-Driven Reanalysis of Exome Sequencing Data From Patients With Inherited Retinal Diseases, 2024

IMPORTANCE Despite advances in next-generation sequencing (NGS), a significant proportion of patients with inherited retinal disease (IRD) remain undiagnosed after initial genetic testing. Exome sequencing (ES) reanalysis in the clinical setting has been suggested as one method for improving diagnosis of IRD. OBJECTIVE To investigate the association of clinician-led reanalysis of ES data, which incorporates updated clinical information and comprehensive bioinformatic analysis, with the diagnostic yield in a cohort of patients with IRDs in Korea.

DESIGN, SETTING, AND PARTICIPANTS This was a multicenter prospective cohort study involving 264 unrelated patients with IRDs, conducted in Korea between March 2018 and February 2020. Comprehensive ophthalmologic examinations and ES analyses were performed, and ES data were reanalyzed by an IRD specialist for single nucleotide variants, copy number variants, mobile element insertions, and mitochondrial variants. Data were analyzed from March to July 2023.

MAIN OUTCOMES AND MEASURES Diagnostic rate of conventional bioinformatic analysis and clinician-driven ES reanalysis.

RESULTS A total of 264 participants (151 [57.2%] male; mean [SD] age at genetic testing, 33.6 [18.9] years) were enrolled, including 129 patients (48.9%) with retinitis pigmentosa and 26 patients (9.8%) with Stargardt disease or macular dystrophy. Initial bioinformatic analysis diagnosed 166 patients (62.9%). Clinician-driven reanalysis identified the molecular cause of diseases in an additional 22 patients, corresponding to an 8.3–percentage point increase in diagnostic rate. Key factors associated with new molecular diagnoses included clinical phenotype updates (4 patients) and detection of previously overlooked variation, such as structural variants (9 patients), mitochondrial variants (3 patients), filtered or not captured variants (4 patients), and noncanonical splicing variants (2 patients). Among the 22 patients, variants in 7 patients (31.8%) were observed in the initial analysis but not reported to patients, while those in the remaining 15 patients (68.2%) were newly detected by the ES reanalysis.

CONCLUSIONS AND RELEVANCE In this cohort study, clinician-centered reanalysis of ES data was associated with improved molecular diagnostic yields in patients with IRD. This approach is important for uncovering missed genetic causes of retinal disease.

Upadhyaya, A. Leber congenital amaurosis: A clinical and genetic study from a tertiary eye care center, 2024

PURPOSE: To assess the clinical phenotypes and genetic mutations in patients with Leber congenital amaurosis (LCA) from a tertiary eye care center in India. Design: Retrospective observational study.

METHODS: The study includes patients with a clinical diagnosis of LCA who underwent genetic testing from January 2016 to December 2021. The clinical exome of the patients was analyzed by targeted next-generation sequencing. The genetic variants found were classified as per standard American College of Medical Genetics and Genomics (ACMG) criteria and ClinVar database.

RESULTS: There were 35 patients (19 females, 16 males) of LCA. Family history was positive in 29% (10/35) and a history of consanguinity was noted in 54% (19/35) of the patients. The mean presenting best-corrected visual acuity was 2.48 ± 0.59 logMAR. Retinal pigment epithelial abnormalities and macular involvement were seen in 83% (58/70) and 23% (16/70) of the eyes, respectively, at presentation. The most common causative genes for LCA in our cohort were: GUCY2D (20%, 7/35), CRB1 (14%, 5/35), RPE65 (11%, 4/35), RPGRIP1 (11%, 4/35), and LCA5 (9%, 3/35). Autosomal recessive inheritance was seen in 94% (33/35). Macular involvement at presentation was seen in CRB1 (3/5), NMNAT1 (2/2), and one each of RPE65, LCA5, and RDH12 patients. The genetic testing cost was reduced from 23,800 INR to 15,000 INR per test in the study duration.

CONCLUSIONS: Genetic screening of LCA cases identified various genotypes, with GUCY2D being the most common. Increased awareness and reduced costs of genetic testing would benefit both patients and caregivers. With promising clinical trial outcomes, genotyping is crucial for better patient selection and treatment.

Morita, R. Vitamin A deficiency presenting with ptosis and optic neuropathy in child with autism spectrum disorder, 2025

PURPOSE: To report our findings in a rare case of vitamin A deficiency (VAD) in a 5-year-old boy who presented with ptosis and exotropia.

METHODS: Comprehensive ophthalmological examinations including full-field electroretinography (ffERG), optical coherence tomography, and magnetic resonance imaging were performed.

RESULTS: The decimal visual acuity was 0.02 in both eyes at the initial examination. Ophthalmological examinations revealed bilateral corneal opacities, conjunctival keratinization, and exotropia. The scotopic ff-ERGs were extinguished and the photopic ff-ERGs were significantly reduced. Blood tests confirmed severe VAD of ≤ 5 IU/dL (normal range, 97–316 IU/dL). Optical coherence tomography (OCT) showed a thinning of the retinal nerve fiber layer, and MRI suggested a narrowing of the optic nerve canals. A detailed medical history identified autism and a highly selective eating habit limited to white rice. Oral vitamin A supplementation (0.6 g/ day) and zinc acetate (25 mg/day) were initiated. Within one month, the corneal epithelial defects had resolved, and the ptosis improved. One year and three months post-treatment, the scotopic and photopic ffERGs were markedly improved. However, the OCT and visual evoked potential findings indicated a persistent optic neuropathy.

CONCLUSIONS: This case underscores the effect of irreversible optic neuropathy due to delayed VAD diagnosis and treatment in a pediatric patient. An early detailed dietary history, electrophysiological screening, and appropriate supplementation are critical tasks that are needed to lessen the risk of irreversible visual impairment in pediatric VAD cases.

Wen, L. Novel CACNA1F pathogenic variant in pediatric incomplete X-linked CSNB: integrating portable ERG and genetic analysis, 2025

PURPOSE: To report a novel hemizygous nonsense variant in the CACNA1F gene associated with congenital stationary night blindness (CSNB) in a pediatric patient, emphasizing the utility of portable electroretinography (ERG) and genetic testing in diagnosing unexplained visual impairments.

METHODS: The patient, a 5-year-old male, underwent comprehensive clinical evaluation, including detailed anterior segment and fundus examinations, full-field electroretinogram (ffERG) using a RETeval™ portable device, and whole exome sequencing (WES) to elucidate the genetic basis of his visual impairment. Structural modeling of the mutated protein was performed using SWISS-MODEL and PYMOL.

RESULTS: Best-corrected visual acuity was 0.4 logMAR bilaterally, with unremarkable anterior segment and fundus examinations. FFERG revealed significant abnormalities consistent with incomplete CSNB: severely reduced rod response in dark-adapted (DA) 0.01, negative waveform with b/a wave ratio < 1.0 in DA 3.0, and diminished cone response in lightadapted ERG. WES identified a novel pathogenic variant in the CACNA1F gene (c.1234G > T, p.E412*), inherited maternally. This variant introduces a premature stop codon at position 412, likely resulting in a truncated CACNA1F protein.

CONCLUSIONS: This case highlights the importance of comprehensive clinical assessments and genetic testing in pediatric patients with unexplained visual impairments, revealing a novel CACNA1F variant that expands our

understanding of CSNB. The use of a portable ERG device proved particularly valuable. in assessing retinal function in this young patient. Further investigations are warranted to elucidate the clinical implications of this novel pathogenic variant.

Keeling, E. Can a Portable Flash Visual Evoked Potential (VEP) Device Identify Chiasmal Decussation Anomalies in Albinism?, 2025

BACKGROUND: Visual evoked potentials (VEPs) are used to detect chiasmal misrouting associated with albinism. However, VEPs are only performed in specialist centres and typically have long waiting lists. The portable electrophysiology device RETeval® shows promise as a clinical screening tool across a range of ophthalmic conditions. Here, we explore its utility in detecting chiasmal abnormalities associated with albinism.

METHODS: Flash VEPs were recorded on the RETeval® and by standard ISCEV techniques for 27 patients with suspected albinism and 40 control patients as part of routine appointments. We retrospectively investigated the agreeability between the two methods. The amplitude/latency of the main component was measured for standard VEPs whilst a correlation value of interhemispheric difference was calculated for the RETeval® data.

RESULTS: We demonstrate a significant difference between albinism patients and controls ($p < 0.001$) with respect to the interhemispheric difference identified by the RETeval®. By applying a threshold of 0.001865 to the correlation value, the RETeval® detected chiasmal misrouting in all 27 patients with albinism and had 97% agreeability to standard testing.

CONCLUSIONS: This study shows the potential of using the RETeval® as a clinical tool for the diagnosis of chiasmal anomalies in albinism. The RETeval® has significant time/cost savings which could hasten diagnoses.

Kwok, X. Evaluating ocular health in retinal gene therapies, 2025

Inherited retinal disease (IRD) refers to a heterogeneous group of genetic eye disease that causes progressive vision loss and was once regarded untreatable. However, regulatory approval for Luxturna (voretigene neparvovec-rzyl) for patients with biallelic mutation in the RPE65 gene has heralded new optimism for patients with the disease. One critical question in designing clinical trial in patients with IRD is choosing appropriate outcome measures to assess the retina, taking into consideration the slow disease progression and the inherent low vision associated with the disease. In this review, the functional and structural endpoints that have been utilised in human retinal gene therapy clinical trials in patient selection as well as measures of safety and efficacy are described. For clinicians, an appreciation of these specialised measures of eye health in a patient with IRD will enhance understanding of retinal health assessments, disease prognosis as well as facilitating discussions with patients potentially eligible for retinal gene therapy clinical trial.

Telukunta, P. CERKL related autosomal recessive retinitis pigmentosa - A report on four affected members from a single family, 2025

This case report describes the phenotypes associated with ceramide kinase like protein (CERKL) retinitis pigmentosa (RP) in a family with four affected members. We performed a cross sectional study of four members from a single family with RP. The retinal features, electrophysiology findings, and genetic results are discussed. Next generation sequencing based genetic testing was performed in two of the four affected family members. The affected individuals consisted of a 42 year old female proband (II.4), her 39 year old sister (II.6), and her two nephews, aged 10 and 12 years (III.2 and III.3, respectively). The genetic testing of III.2 and III.3 revealed the presence of a pathogenic homozygous frameshift nonsense variant (c. 1045_1046delAT, p.Met349Valfs*19) in exon 7 of the CERKL gene. All four family members had central vision problems since childhood. The best corrected visual acuity of the young patients, III.2 and III.3, was 20/30 and 20/80, respectively. The older patients (II.4 and II.6) were able to perceive only hand movements at the time of examination. The common retinal features found in III.2 and III.3 at presentation were minimal optic disc pallor, arteriolar attenuation, early loss of macular photoreceptors, central scotomas, and near extinguished responses in full field electroretinogram (ERG). There were no pigmentary or chorioretinal atrophic changes in the retina noted in individuals III.2 and III.3. The common retinal features in the proband (II.4) and her sister (II.6) in their 5th and 4th decades were prominent vascular attenuation, optic disc pallor, total macular atrophy, peripheral bony spicule pigmentation/scalloped chorioretinal atrophic patches, and a nondetectable ERG. In conclusion, the study of this family highlights the possibility of a severe phenotype in autosomal recessive CERKL related RP due to the nonsense variant c. 1045_1046delAT, p.Met349Valfs*19, as observed in our two genetically confirmed patients. Identifying the retinal phenotype and specific pathogenic variant is essential for accurate genetic counselling, personalized visual rehabilitation, and potential targeted therapies.

Vempuluru, V. High-dose intravitreal topotecan (100 mcg/0.1cc) as monotherapy for recurrent/refractory intraocular retinoblastoma in seven eyes, 2025

PURPOSE: To report the outcomes and safety of 100 mcg/0.1cc intravitreal topotecan (IVitT100) as monotherapy for refractory/recurrent intraocular retinoblastoma (RB).

METHODS: Retrospective single-center study of 7 RB patients who received IVitT100 as monotherapy between January 2024 and December 2024 with a minimum follow-up of 3 months after the last injection.

RESULTS: At presentation, six eyes were classified as Group D and one as Group C, according to the International Classification of Retinoblastoma. High-dose topotecan was administered for refractory and recurrent disease in 2 (29%) and 5 (71%) eyes, respectively. The active disease was in the form of a intraretinal tumor with vitreous seeds (n=3, 43%), intraretinal tumor with epiretinal seeds (n=1, 14%), isolated intraretinal tumor (n=1, 14%), isolated subretinal seeds (n=1, 14%), or isolated vitreous seeds (n=1, 14%). At a mean follow-up of 7 months (median, 6 months; range, 3 to 10) from the last injection of IVitT00, tumor control was achieved in 100% (4 of 4) eyes with vitreous seeds, 100% (1 of 1) with epiretinal seeds, 100% (1 of 1) with subretinal seeds, and 60% (3 of 5) with retinal tumor. Overall, tumor control was achieved in 5 eyes (71%) with IVitT100 monotherapy. Additional treatments were warranted in 2 eyes for complete tumor control. Globe salvage was achieved in all eyes (100%). The electroretinogram (n=4) showed no significant changes compared to the baseline.

CONCLUSION: IVitT100 is a safe option for refractory or recurrent intraocular RB and holds promise for controlling refractory vitreous seeds, subretinal seeds, and intraretinal tumors.

Zobor, D. Applicability of Electroretinography Measurements in Congenital PAX6-Related Aniridia, 2025

PURPOSE: Congenital PAX6-aniridia is associated with ocular developmental abnormalities, including photoreceptor specification. We focused on characterizing retinal function by electroretinography (ERG) measurements and evaluated the usefulness of a handheld electrophysiology tool.

METHODS: Patients underwent a comprehensive ophthalmological examination including best corrected visual acuity (BCVA) and full-field ERG measurements using the RETeval system with sensor strip skin electrodes. In addition to International Society for Clinical Electrophysiology of Vision (ISCEV) standards, photopic negative responses (PhNRs) were recorded.

RESULTS: Forty-one eyes of 21 patients (10 and 11 male patients, age = 25.3 ± 16.9 years, range = 9–60 years) from 16 families were included. BCVA ranged from light perception to 0.3 logMAR (mean = 1.02 ± 0.54) and exhibited greater impairment in older patients. Despite considerable variability in ERG amplitudes, no statistically significant difference was observed in ERG amplitudes between patients and controls (n = 18). However, implicit times (ITs) were significantly delayed ($P < 0.001$). Although PhNR response amplitudes and ITs were not significantly different from controls, W-ratio was considerably lower in patients (W = 0.89 ± 0.1) than in controls (W = 1.09 ± 0.05), indicating reduced signal transmission through the different layers of the retina. We observed an effect of glaucoma status causing even lower W-ratios (W = 0.94 ± 0.13 without confirmed glaucoma; and W = 0.88 ± 0.11 with treated glaucoma). ERG recordings were well-tolerated.

CONCLUSION: This is the largest ERG study conducted in congenital aniridia. Results show that both photoreceptor-related functions and postreceptoral signal transmission are affected in PAX6-related aniridia, suggesting retinal changes beyond the central macula. RETeval can serve as a useful instrument for the evaluation and surveillance of retinal function in aniridia, underscoring the potential risk of glaucoma.

Lu, J. Novel mutation in CNNM4 gene in a Chinese family with Jalili syndrome and literature review, 2025

AIM: To report two cases of Jalili syndrome (JS) harboring a novel mutation in the CNNM4 gene, review previously published studies on JS, and analyze factors potentially associated with visual acuity in patients with JS.

METHODS: Two JS patients from a non-consanguineous Chinese family underwent comprehensive ophthalmic evaluations. Next-generation sequencing (NGS) was performed to identify pathogenic variants, and Sanger sequencing was used for validation. A literature search was conducted to retrieve studies on JS published up to January 31, 2025; only studies with detailed records of visual acuity and mutation sites were included. Correlations between visual acuity and age, as well as between visual acuity and mutation domain, were analyzed.

RESULTS: A total of 53 patients with detailed visual acuity and mutation site records from previous studies were included in the analysis. The mean logarithm of the minimum angle of resolution (logMAR) visual acuity was 1.15 (range: 0.69-2.00). Spearman's correlation analysis showed a positive correlation between visual acuity (logMAR) and age ($r_s=0.502$, $P<0.001$). No association was found between logMAR visual acuity and mutation domain ($P=0.748$). The 6-year-old proband and her 3-year-old brother carried a novel homozygous missense variant c.949A>C

(p.Ser317Arg) in CNNM4. Both patients presented with reduced visual acuity, pendular nystagmus, photophobia, night blindness, color vision loss, macular atrophy, and amelogenesis imperfecta. Optical coherence tomography (OCT) revealed atrophy of the outer retinal layers, and electroretinography (ERG) showed extinguished cone and rod responses. Fundus autofluorescence (FAF) and fundus fluorescein angiography (FFA) of the proband demonstrated bilateral retinal pigment epithelium (RPE) defects around the optic disc, vascular arcades, and macular region. At the latest follow-up (30mo), the proband's condition remained stable: best-corrected visual acuity was 2.00 logMAR (right eye) and 1.30 (left eye), with no changes in fundus appearance. The younger brother had a best-corrected visual acuity of 1.52 logMAR in both eyes at the latest follow-up, accompanied by severe bilateral macular atrophy and obvious dentin discoloration due to progressive enamel thinning.

CONCLUSION: This study reports a novel homozygous missense variant c.949A>C (p.Ser317Arg) in CNNM4 in a Chinese JS family. Visual acuity in JS patients deteriorates with increasing age.

Lin, X. Role of additional topotecan injections (plus two) in reducing recurrence rate in retinoblastoma of group D and group E patients: a retrospective study, 2025

OBJECTIVE To evaluate the effectiveness of administering additional intravitreal topotecan injections (plus two) in reducing the recurrence rate in patients with advanced retinoblastoma (RB).

METHODS AND ANALYSIS This retrospective, noncomparative and interventional study encompassed 26 eyes of 25 patients with RB, treated between January 2019 and April 2024. All eyes in this series had received previous intravenous chemotherapy and/or intraarterial chemotherapy. Patients received intravitreal topotecan (30 µg/0.1 mL) and/or intravitreal melphalan (20–30 µg/0.1 mL) injections every 3–4 weeks until vitreous seeds regression was achieved. Subsequently, two additional injections of topotecan (30 µg/0.1 mL) were administered after complete regression to consolidate subclinical residuals. The control of vitreous seeds, ocular toxicity assessment and clinical characteristics was observed.

RESULTS The median age of the patients was 26 months, with 57.7% belonging to group D and 42.3% to group E of RB classification. A total of 111 injections were administered in 26 eyes, with a median of 4 injections per eye. Complete vitreous seeds regression was achieved in 100% of eyes, and eye salvage was successful in 24 of 26 eyes (92.3%). There were no recurrences of vitreous seeds. Enucleation was performed in two eyes: one due to phthisis bulbi and one due to optic nerve tumour recurrence. No cases of systemic metastasis or death were reported.

CONCLUSION Administering additional intravitreal topotecan injections (plus two) following the complete regression of vitreous seeds may contribute to reducing the recurrence rate in patients with RB. This approach enhances the long-term efficacy of intravitreal injections, thereby contributing to higher eye salvage rates. However, the retrospective, non-randomised design and small sample size remain limitations. Multicentre prospective studies are warranted to validate these findings and refine treatment protocols.

Dhamankar, T. First Genetically Confirmed Case of CABP4-Related Cone-Rod Synaptic Disorder from India, 2026

CABP4-related retinal dysfunction (MIM: 610427) is a rare autosomal recessive disorder caused by pathogenic variants in CABP4, a photoreceptor synaptic calcium-binding protein. Initially classified as incomplete congenital stationary night blindness (icCSNB) due to an electronegative scotopic electroretinogram (ERG),[1] it is now recognized as a congenital cone-rod synaptic disorder (CRSD) characterized by predominant cone dysfunction with relatively preserved rod activity.[2,3] We report the first genetically confirmed case of CABP4-related CRSD from India.

Fathy, N. A Novel Variant in the G-Protein Receptor Kinase (GRK1) Causes Oguchi Syndrome, Type II, in an Egyptian Family, 2026

OBJECTIVE This study aimed to report the clinical, electrophysiological, and genetic findings in two siblings of an Egyptian family with type 2 Oguchi disease, with multimodal imaging performed for proper evaluation.

METHODS Two siblings of consanguineous parents presented with poor night vision underwent full ophthalmological examination, ultra-widefield fundus photography, fundus autofluorescence (FAF) and spectral-domain optical coherence tomography (SD-OCT) of the macula, repeated fundus photography following dark adaptation for 3 hours and electroretinogram (ERG). Exome sequencing (ES) was performed for one patient and Sanger sequencing was then used for segregation analysis.

RESULTS The clinical findings and investigations were suggestive of the Oguchi disease phenotype. The ES revealed a homozygous stop gain variant, first time to be detected in Ouchi II patient, in exon 6 of the G-protein receptor kinase 1 (GRK1) gene, c.1338c>A: p.Cys446Ter.

CONCLUSIONS These are the first molecularly confirmed patients from Egypt with Oguchi disease type 2. In addition, we identified a pathogenic GRK1 variant first time to be detected in Oguchi II patients expanding both the phenotypic and mutational spectrum of Oguchi disease.

Naveen, P. Severe early-onset retinal and lenticular abnormalities associated with homozygous c.575T>C (p.Ile192Thr) variants in the VSX2 gene, 2026

OBJECTIVE To describe the clinical, imaging, electrophysiologic, and genetic characteristics associated with a novel homozygous VSX2 missense variant presenting with retinal and lenticular abnormalities.

METHODS: A case series of five affected individuals from four unrelated families with early-onset visual impairment and nystagmus was evaluated. All patients underwent detailed ophthalmic examination, multimodal retinal imaging including fundus photography and fundus autofluorescence, and full-field electroretinography (ERG). Genetic analysis was performed to identify the underlying molecular defect.

RESULTS: All affected individuals demonstrated superior lens subluxation, frequently associated with early-onset cataract. Fundus examination revealed myopic tessellated fundi, tilted optic discs, peripheral avascular retina, and circular macular excavations resembling pseudocoloboma. Fundus autofluorescence imaging demonstrated a characteristic triangular hypoautofluorescent pattern along the optic fissure, with hyperautofluorescent borders in four eyes. Full-field ERG revealed severe generalized retinal dysfunction in all evaluated eyes. Genetic analysis identified a homozygous VSX2 missense variant (c.575T>C; p.Ile192Thr) in exon 3, with unaffected parents being heterozygous carriers, consistent with autosomal recessive inheritance. The variant lies within the highly conserved homeodomain and is predicted to disrupt DNA binding and transcriptional regulation of retinal developmental genes.

CONCLUSION: This novel VSX2 variant is associated with a distinctive phenotype characterized by pan-retinal dysfunction and anterior segment abnormalities without classic microphthalmia, expanding the phenotypic spectrum of VSX2-associated disease and highlighting the importance of recognizing this entity for timely diagnosis and management.

Nishina, S. Novel Biallelic CDK9 Variants Are Associated with Retinal Dystrophy without CHARGE-like Malformation Syndrome, 2026

Cyclin-dependent kinase 9 (CDK9) phosphorylates the C-terminal domain of RNA polymerase II (RNAPII) to regulate transcription. Previously, we reported that an 8-year-old boy with the biallelic CDK9 variants p.A288T and p.R303C exhibited a CHARGE-like malformation syndrome in which retinal dystrophy was a distinguishing feature. This dystrophy was caused by the decreased CDK9 kinase activity associated with these variant alleles [wild-type (WT) > A288T > R303C]. In this study, we describe a female patient who also bears biallelic CDK9 variants but displays retinal dystrophy without a CHARGE-like malformation syndrome. Trio-based whole-exome sequencing identified a new variant CDK9 allele, p.P321S, that occurred de novo in the patient. As a result, this female patient displayed compound heterozygous variants composed of the p.A288T CDK9 variant of maternal origin plus the novel p.P321S variant. With respect to reduced kinase activity, the new variant could be ranked as WT > P321S > A288T. Thus, our study raises a possibility that retinal dystrophy can arise with or without a CHARGE-like malformation syndrome depending on the level of kinase activity associated with the combination of variant CDK9 alleles present.

Raji, S. RPGR ORF15 Variants Causing X-Linked Cone Dystrophy, 2026

IMPORTANCE Recent insights into impaired glutamylation caused by distal truncating variants in RPGR ORF15 and its association with the cone-dominated phenotype have provided the first molecular evidence of a genotype-phenotype correlation in male individuals with X-linked RPGR-related retinal dystrophy, though this correlation remains unexplored in female carriers.

OBJECTIVE To characterize the clinical phenotype in female carriers of RPGR variants causing X-linked cone dystrophy in hemizygous male individuals.

DESIGN, SETTING, AND PARTICIPANTS This case-control study was conducted at a specialist genetics clinic from May to December 2024. A total of 11 patients were examined, including female carriers with RPGR variants causing cone dystrophy (n = 7) and age-similar female carriers of RPGR variants causing rod-cone dystrophy as controls (n = 4).

EXPOSURES RPGR variants associated with X-linked cone dystrophy in hemizygous male individuals.

MAIN OUTCOMES AND MEASURES Results of ophthalmic examination, multimodal retinal imaging, and functional testing.

RESULTS Seven female carriers aged 11 to 71 years were identified from RPGR cone dystrophy pedigrees. Visual acuity ranged from 6/4.8 to 6/7.5 (Snellen, 20/16 to 20/25), and 4 of the 7 participants experienced photophobia. Myopia and high cylindrical powers were common (6/7 [86%]), with myopia greater than −6.00 D in 2 patients.

Fundus autofluorescence imaging revealed a diffuse, granular hyperautofluorescence pattern limited to the posterior pole, compared with the typical spoke pattern that extended into the far periphery in female carriers from RPGR rod-cone pedigrees. Green reflectance imaging most sensitively detected an abnormality in the form of an en face tapetallike sheen, which colocalized with a hyperreflective outer retinal band observed on optical coherence tomography. Ultra-widefield retinal imaging demonstrated no peripheral abnormalities. A mosaic pattern of reduced retinal sensitivity was found within the central 20° on microperimetry, which did not correlate with features observed on retinal imaging. Normal rod responses were measured on electroretinography, but average cone responses were 60.1% of the lower normal limit compared with 36% in male probands.

CONCLUSIONS AND RELEVANCE This study identified a distinct phenotype in female carriers of RPGR variants causing X-linked cone dystrophy. In this cohort, the phenotype was consistent with mild cone dysfunction and anatomical macular changes. Depending on X-inactivation skew and rate of disease progression, some female carriers may be suitable for emerging gene therapies currently in clinical trials for affected male individuals.

Takács, A. CDHR1-Associated Retinal Dystrophies: Expanding the Clinical and Genetic Spectrum with a Hungarian Cohort, 2026

AIM: To report on the clinical and genetic spectrum of retinopathy associated with CDHR1 variants in a Hungarian cohort.

METHODS: A retrospective cohort study was conducted at a single tertiary care referral center. The study enrolled nine patients harboring biallelic variants in the CDHR1 gene. Detailed clinical history, multimodal imaging, electroretinography, and molecular genetics are presented.

RESULTS: We identified four CDHR1 variants predicted to cause loss-of-function and five phenotypes (cone dystrophy, central areolar choroidal dystrophy, cone-rod dystrophy, rod-cone dystrophy, and late-onset macular dystrophy). The most frequent variant was the synonymous CDHR1 c.783G>A (p.Pro261=) variant (10/18 alleles, 55.6%). A novel splice acceptor site variant, CDHR1 c.349-1G>A, and a novel intronic variant, CDHR1 c.1168-10A>G, were also detected. Fundus examination revealed macular atrophy with or without peripheral retinal changes. Full-field electroretinography, available in seven patients, demonstrated decreased light-adapted and extinguished dark-adapted responses in both the rod-cone dystrophy group and patients with macular involvement. OCT imaging indicated ellipsoid zone disruption with foveal sparing in two out of nine patients and severe retinal damage in rod-cone dystrophy cases.

CONCLUSIONS: The predominant clinical manifestations of cone dystrophy, cone-rod dystrophy, and macular dystrophy in the Hungarian patient cohort showed heterogeneity, with a rod-cone dystrophy phenotype observed in five of nine cases (55.6%). The natural history of CDHR1-associated retinopathy typically follows a slow progression, providing a therapeutic window, which makes the disease a candidate for gene therapy.

Tsutsumi, N. Long-term follow-up of a Tay-Sachs disease patient with cherry-red spot, 2026

PURPOSE To describe the clinical progression and ophthalmic findings in a Japanese boy with Tay-Sachs disease at ages 5 and 8 months.

RESULTS The patient was born at 38 weeks of gestation and developed normally until motor skill delays were identified at age 1 year and 1 month. At that time, brain magnetic resonance imaging revealed diffuse T2 hyperintensity in the bilateral basal ganglia. At age 1 year and 6 months, he was able to fix and follow objects, and the optic discs appeared normal, but bilateral cherry-red spots were observed in the maculae. Based on these findings, together with hypersensitivity to sound and markedly reduced β-hexosaminidase A activity, Tay-Sachs disease was biochemically diagnosed. By age 2 years and 1 month, the patient had lost the ability to fixate on and follow objects. Fundoscopy at age 4 years and 4 months revealed optic atrophy and reduced cherry-red spots, electroretinography (ERG) at age 4 years and 9 months showed a complete loss of retinal responses, and optical coherence tomography at age 5 years and 3 months demonstrated retinal thinning. Long-term observation revealed progressive degeneration, consistent with previous reports. Lipid deposition in all retinal layers was considered to contribute to retinal atrophy.

CONCLUSIONS This report highlights progressive retinal degeneration with optic atrophy, retinal thinning, and reduction in cherry-red spots. The flat ERG waveform in this patient suggests more advanced retinal involvement than in previous reports and provides insights into the ocular manifestations of Tay-Sachs disease.

ROP

Tekavcic Pompe M. et al. Flicker electroretinogram recorded with portable ERG device in prematurely born schoolchildren with and without ROP, 2019

PURPOSE: The purpose of this study was to compare electroretinographic (ERG) responses of preterm schoolchildren, with and without a history of retinopathy of prematurity (ROP) with those of full-term schoolchildren by using a portable ERG device (RETeval system).

METHOD: Twenty five prematurely born schoolchildren with a mean gestational age of 27 + 1/7w (range 23–30w) and a mean birth weight of 1030 g (range 580–1700 g) who were 6.9 ± 2.2 years old participated in the study (premature group). A further subdivision according to a history of ROP (ROP+ group) or its absence (ROP- group) was introduced. Twenty-eight healthy full-term schoolchildren with an average age of 8.6 ± 1.9 years participated as the control group. 30-Hz flicker ERG responses were obtained, and implicit times and amplitudes were compared between the groups.

RESULTS/ CONCLUSION: Prematurely born schoolchildren exhibit longer implicit time of the 30-Hz flicker ERG response compared to controls, suggesting a possible abnormality of the retinal cone system function. Under such circumstances, portable ERG device might be used clinically as a screening tool for retinal function evaluation in prematurely born children.

Hansen et al. Flicker electroretinogram in newborn infants, 2022

PURPOSE: To develop and validate a flicker electroretinogram (ERG) protocol in term-born neonates as a potential tool for assessing preterm infants at risk of developing retinopathy of prematurity.

METHODS: A custom flicker ERG protocol was developed for use with the hand-held RETeval® electrophysiology device. Feasibility of measuring flicker ERG through closed eyelids and without mydriasis was established in a pilot study enabling optimisation of the test protocol. Following this, healthy termborn neonates (gestational age 37–42 weeks) were recruited at the Neonatology clinic of the University Hospital Zurich. Flicker ERG recordings were performed using proprietary disposable skin electrodes during the first four days of life when the infants were sleeping. Flicker stimuli were presented at 28.3 Hz for a stimulus series at 3, 6, 12, 30, and 50 cd·s/m2, with two measurements at each stimulus level. Results were analysed offline. Flicker ERG peak times and amplitudes were derived from the averaged measurements per stimulus level for each subject.

RESULTS: 28 term-born neonates were included in the analysis. All infants tolerated the testing procedure well. Flicker ERG recording was achieved in all subjects with reproducible flicker ERG waveforms for 30 and 50 cd·s/m2 stimuli. Reproducible ERGs were recorded in the majority of infants for the weaker stimuli (with detectable ERGs in 20/28, 25/28, and 27/28 at 3, 6, and 12 cd·s/m2, respectively). Flicker ERG amplitudes increased with increasing stimulus strength, with peak times concurrently decreasing slightly.

CONCLUSION: Flicker ERG recording is feasible and reliably recorded in sleeping neonates through closed eyelids using skin electrodes and without mydriasis. Flicker ERG amplitude decreases for lower luminance flicker but remains detectable for 3 cd·s/m2 flicker in the majority of healthy term-born neonates. These data provide a basis to study retinal function in premature infants using this protocol.

Jeong et al. Evaluation of Electroretinograms Using RETeval™ in Preterm Infants without retinopathy of Prematurity, 2022

PURPOSE: This study was conducted to evaluate the usefulness of light adapted electroretinography (ERG) using the RETevalTM system (LKC Technologies, Gaithersburg, MD, USA) in preterm infants without retinopathy of prematurity.

METHODS: Overall, 18 preterm infants underwent light adapted ERG using the RETevalTM system without sedation. Readable results were acquired from 11 patients (61%) and the mean gestational age at birth was 33 ± 3 weeks.

RESULTS: The amplitude and implicit time of the 'a' wave was -8.1 ± 6.6 μV and 17.3 ± 7.8 ms, respectively, while those of the 'b' wave was 20.4 ± 13.6 μV and 36.7 ± 8.8 ms, respectively. Additionally, 30-Hz flicker results were obtained with an amplitude and implicit time of 6.0 ± 3.8 μV and 32.3 ± 2.8 ms, respectively. Negative correlation was found between the 'a' wave amplitude and age at examination ($p < 0.05$). The light-adapted 3.0 ERG response was decreased in preterm infants and a larger decrease in 'b' wave amplitude than 'a' wave amplitude was observed, which corresponds to the histological maturation of the retina.

CONCLUSIONS: Our study indicates that RETevalTM system is useful for evaluating retinal function in preterm infants.

Taner, A. Flicker electroretinogram in preterm infants, 2024

BACKGROUND: Infants born prematurely are at risk of developing retinopathy of prematurity, which is associated with abnormalities in retinal function as measured using electroretinography. The aim of this study was to record non-invasive flicker electroretinograms (ERGs) in preterm infants and compare function of moderate and very or extremely preterm infants.

METHODS: In this non-randomized, cross-sectional study, 40 moderate preterm (gestational age (GA) 34 0/7 to 36 6/7 weeks, Group A) and 40 very or extremely preterm infants (GA ≤ 31 weeks, Group B) were recruited for flicker ERG recording through closed eyelids using the RETeval® device and skin electrodes. Group A was tested within the first week of life and Group B between 34th and 37th week postmenstrual age. Flicker stimuli were presented at 28.3 Hz with stimulus levels of 3, 6, 12, 30 and 50 cd•s/m 2. Primary endpoints were peak time (ms) and amplitude (μV).

RESULTS: Flicker ERGs were recordable in most infants with the highest proportion of reproducible ERGs at 30 cd•s/m 2. Amplitudes increased with stronger flicker stimulation, while peak times did not differ significantly between stimulus levels nor groups. Amplitudes were significantly greater in Group B at the strongest stimulus level (Mann-Whitney-U-Test=198.00, Z =∠4.097, p =∠<0.001).

CONCLUSIONS: Feasibility of collecting flicker ERG data in most preterm infants was confirmed. We found no evidence of reduced retinal responses to flicker stimuli associated with extreme prematurity. Higher amplitudes in very and extremely preterm infants could indicate acceleration of retinal development following birth, triggered by visual stimulation.

Sisera, L. The effect of high-dose erythropoietin perinatally on retinal function in school-aged children born extremely or very preterm, 2024

PURPOSE: To investigate the long-term effects of high-dose recombinant human erythropoietin (rhEPO) administered during the perinatal period on retinal and visual function in children born extremely or very preterm.

DESIGN: Randomized, double-blind clinical trial follow-up plus cohort study.

METHODS: Setting: Department of Ophthalmology, University Hospital Zurich, Zurich, Switzerland.

STUDY POPULATION: Extremely or very preterm-born children aged 7-15 years, previously randomized to receive either high-dose rhEPO or placebo in the perinatal period. Inclusion criteria: participation in an ongoing neuropediatric study (EpoKids), written informed consent (IC). Exclusion criteria: previous ocular trauma or surgery; retinal or developmental disease unrelated to prematurity. Healthy control (HC) children of comparable age were recruited. Inclusion criteria: term birth, IC. Exclusion criteria: any ocular/visual abnormality, high refractive error. Intervention status (rhEPO/placebo) was unknown to examiners and subjects at examination, with examiners unblinded only after completion of all analyses.

OBSERVATION PROCEDURES: Electroretinography (ERG) was performed with the RETeval device (LKC Technologies, Inc., Gaithersburg MD). Ophthalmological and orthoptic examinations excluded comorbidity in the prematurely born cohort and ocular diseases in the HC group.

MAIN OUTCOME MEASURES: Scotopic and photopic ERG response amplitudes and peak times (6 amplitudes; 6 peak times). Secondary outcomes were habitual visual acuity and color discrimination performance (for descriptive summary only).

RESULTS: No differences in ERG parameters between EPO (n=52; 104 eyes) and placebo (n=35; 70 eyes) subgroups were observed (all corrected p>0.05). Two cone system-mediated peak times were slightly slower in the placebo than HC (n=52; 104 eyes) subgroup (coefficient/95% confidence interval (CI) = 0.53/0.21 to 0.85 and 0.36/0.13 to 0.60; p = 0.012 and 0.022); a predominantly rod system-mediated peak time was slightly faster in the EPO than the HC subgroup (coefficient/95% CI = -4.33/-6.88 to -1.78; p = 0.011). Secondary outcomes were comparable across subgroups.

CONCLUSIONS: Administration of high-dose rhEPO to infants born extremely or very preterm during the perinatal period has no measurable effects on retinal function in childhood compared to placebo. Premature birth may cause small, likely clinically insignificant effects on retinal function in childhood, which may be partially mitigated by administration of rhEPO during the perinatal period.

Myopia

Zabochnicki, M. When a large refractive error is found in children, should we immediately order electroretinography?, 2023

Electroretinography is a useful tool used in diagnosing retinal disorders. Refractive errors are a common and increasing group of abnormalities, which, if undiagnosed, may lead to complications. Physiologically, i.e., refraction of the child's eye, evolves from myopic or hyperopic after birth, towards emmetropic. However, high refractive errors tend to present with retinal diseases. Early electroretinography is a great diagnostic test that allows its detection. Because of that, it can help avoid loss of eyesight and prevent future implications. Unfortunately, low accessibility and interpretational difficulties are main barriers in wider implementation of that method.

Huang, l. High myopia is common in patients with X-linked Retinopathies, 2024

OBJECTIVE: High myopia can occur as a single or syndromic condition. The aim of this study was to evaluate the refractive error and myopic maculopathy in patients with X-linked retinopathies.

METHODS: Whole exome sequencing, Sanger sequencing, and comprehensive ocular examinations were performed in patients with X-linked retinopathies.

RESULTS: A total of 17 patients were recruited, including six with CACNA1F, seven with RPGR, three with NYX, and one with OPN1MW mutations. The diagnoses were congenital stationary night blindness (6), cone–rod dystrophy (4), retinitis pigmentosa (4), achromatopsia (1), Leber congenital amaurosis (1), and myopia (1). Myopia was present in 88.2% patients, and 64.7% patients had high myopia. Gene analysis showed that high myopia was present in 80% patients with CACNA1F, 100% patients with NYX, and 57.1% patients with RPGR mutations. In the ATN classification, 64.7% of the patients were A1T0N0 and 35.3% were A0T0N0. The refractive errors progressed over time, even in patients with congenital stationary night blindness. Two females with heterozygous de novo RPGR mutations presented with retinitis pigmentosa or cone rod dystrophy combined with high myopia.

CONCLUSION: High myopia is common in patients with X-linked retinopathies, and myopic maculopathy was only mild atrophy without traction and neovascularization.

Cho et al. Factors Related to Axial Length Elongation in Myopic Children Who Received 0.05% Atropine Treatment, 2022

PURPOSE: To evaluate the longitudinal changes of axial length (AL) and factors associated with AL growth in myopic children receiving 0.05% atropine.

METHODS: This single-center retrospective study included children aged 4–13 years with myopia of at least -0.5 diopters (D) treated with 0.05% atropine eye drops from November 2016 to May 2021. Predictive factors for AL change were evaluated using linear mixed models.

RESULTS: Among 109 patients (218 eyes), 58 (53.2%) were male and the mean age at treatment was 8.5 – 2.0 years. At baseline measurement, the mean spherical equivalent was -4.05 – 2.34 diopters (D), and AL was 25.00 – 0.97 mm. The mean follow-up duration was 25.4 (12–58) months, and the mean AL elongation was 0.23 – 0.17 mm/year during the follow-up periods. AL shortening of ‡0.05 mm at subsequent visit occurred in 18 patients (26 eyes). The mean AL change in the group without initial AL shortening was statistically larger than that in the group with initial AL shortening (0.26 – 0.16 mm/year vs. 0.02 – 0.17 mm/year, P < 0.001). In linear mixed model, the age at atropine treatment and initial AL shortening were significantly associated with respect to AL growth (beta coefficient: -0.032 and -0.122, respectively, P < 0.001 for both).

CONCLUSIONS: Our study found that older age and initial AL shortening are predictors of favorable response after 0.05% atropine treatment. Children with AL shortening at initial subsequent visit may be associated with good long-term response, and younger children may require higher concentration of atropine for optimal response.

Barboni, M. Pupillary Light Reflex Reveals Melanopsin System Alteration in the Background of Myopia-26, the Female Limited Form of Early-Onset High Myopia, 2024

PURPOSE. The purpose of this study was to evaluate pupillary light reflex (PLR) to chromatic flashes in patients with early-onset high-myopia (eoHM) without (myopic controls = M-CTRL) and with (female-limited myopia-26 = MYP-26) genetic mutations in the ARR3 gene encoding the cone arresting.

METHODS. Participants were 26 female subjects divided into 3 groups: emmetropic controls (E-CTRL, N = 12, mean age = 28.6 ± 7.8 years) and 2 myopic (M-CTRL, N = 7, mean age = 25.7 ± 11.5 years and MYP-26, N = 7, mean age = 28.3 ± 15.4 years) groups. In addition, one hemizygous carrier and one control male subject were examined. Direct PLRs were recorded after 10-minute dark adaptation. Stimuli were 1-second red (peak wavelength = 621 nm) and

blue (peak wavelength = 470 nm) flashes at photopic luminance of 250 cd/m2. A 2-minute interval between the flashes was introduced. Baseline pupil diameter (BPD), peak pupil constriction (PPC), and postillumination pupillary response (PIPR) were extracted from the PLR. Group comparisons were performed with ANOVAs.

RESULTS. Dark-adapted BPD was comparable among the groups, whereas PPC to the red light was slightly reduced in patients with myopia (P = 0.02). PIPR at 6 seconds elicited by the blue flash was significantly weaker (P < 0.01) in female patients with MYP-26, whereas it was normal in the M-CTRL group and the asymptomatic male carrier.

CONCLUSIONS. L/M-cone abnormalities due to ARR3 gene mutation is currently claimed to underlie the pathological eye growth in MYP-26. Our results suggest that malfunction of the melanopsin system of intrinsically photosensitive retinal ganglion cells (ipRGCs) is specific to patients with symptomatic MYP-26, and may therefore play an additional role in the pathological eye growth of MYP-26.

Fehér T. Cone dysfunction in ARR3-mutationassociated early-onset high myopia: an electrophysiological study, 2024

PURPOSE. Myopia-26, a Mendelian form of early-onset high-myopia (eoHM) caused by mutations in the X-chromosomal ARR3 gene and predominantly affecting females, curiously, may provide an alternative route of investigation to unveil retinal mechanisms underlying pathological eye growth. We conducted a case-control crosssectional prospective electrophysiological study in genetically characterized Myopia-26 patients (ARR3 heterozygous symptomatic females) compared with high myopes harboring intact ARR3 alleles and one carrier hemizygous male.

RESULTS. Participants were 26 volunteers: 10 healthy control females (E-CTRL, mean age = 31.5± 8.8 years), one healthy control male, one carrier male of the mutant ARR3 allele and 14 female eoHM patients (mean age = 27.0± 13.1 years) divided in two groups: seven without (M-CTRL) and seven with (MYP-26) genetic alteration in the ARR3 gene. The clinical evaluation included complete eye screening and full-field electroretinograms (ERGs) recorded from both eyes under mydriasis. Spherical equivalent was comparable (mean=-9.55 ± 2.46 and −10.25 ± 3.22 for M-CTRL and MYP26, respectively) and best corrected visual acuity (BCVA) was significantly different between M-CTRL and MYP-26 (1.0 vs. 0.406 ± 0.253, respectively). E-CTRL and M-CTRL showed similar light-adapted flash and flicker ERG amplitudes; however, the prior values were reduced by ~ 35% (a- and b-waves alike), the latter by ~ 55% in the MYP-26 group ($F(2, 45) > 21.821$, $p < 0.00001$). Dark-adapted a-wave amplitudes were slightly reduced (by ~20%) in all myopic patients compared to E-CTRL, irrespective of the ARR3 genotype (E-CTRL vs. eoHM, p = 0.038)..

CONCLUSIONS. L/M-cone abnormalities due to ARR3 gene mutation is currently claimed to underlie the pathological eye growth in MYP-26. Our results suggest that malfunction of the melanopsin system of intrinsically photosensitive retinal ganglion cells (ipRGCs) is specific to patients with symptomatic MYP-26, and may therefore play an additional role in the pathological eye growth of MYP-26.

Stapley V. Measuring differences in the ERG in myopia using the RETeval device with skin electrodes, 2025

PURPOSE. Previous research suggests that the electroretinogram (ERG) is reduced and delayed in non-pathological myopia. However, the invasive nature of the electrode and cumbersome equipment required has prevented the widescale uptake of ERG measures. This study investigated whether previously reported changes to the ERG response in myopia are also observable when measured using non-invasive skin electrodes and a hand-held ERG device.

METHODS. Monocular flash ERGs were measured using the RETeval® device according to the 'ISCEV 6 Step Dark First cd' protocol in 46 participants with non-pathological myopia (spherical equivalent refraction [SER] −0.50 to −11.25 D, median −3.75 D, median axial length [AL] 25.4 mm) and 47 non-myopic controls (SER +2.00 to −0.25 D, median +1.00 D, median AL 23.6 mm). Measures were performed under pupil mydriasis with Sensor Strip skin electrodes.

RESULTS. The median implicit time for all dark-adapted (DA) components was longer among myopes. Following Holm-Bonferroni correction, this difference reached statistical significance ($p < 0.05$) for the DA 3.0 A-wave, DA 10.0 A-wave and B-waves, and DA Oscillatory potentials 1 and 2. There were no significant differences between median light-adapted (LA) implicit times nor response amplitudes between refractive groups. For all DA components, there was a significant, positive correlation between AL and implicit time (all $p < 0.05$).

CONCLUSIONS. The RETeval®, used with skin electrodes, did not detect the reduction in ERG amplitude reported in myopic eyes using traditional ERG setups, potentially due to high inter-subject variability and/or anatomical confounders associated with the use of a skin electrode. The RETeval® with skin electrodes did detect subtle delays to DA implicit times previously reported in myopia, with a positive relationship observed between AL and implicit time for all DA components. In contrast, no significant differences were observed for LA implicit times, which may indicate underlying differences in the dark-adaptation process and/or scotopic visual pathways in myopia.

Cataracts

Miura G. et al. Effects of cataracts on flicker electroretinograms recorded with RETeval system: new mydriasis-free ERG device, 2016

PURPOSE: The purpose of this study was to evaluate the effects of cataracts on the flicker Electroretinograms (ERGs) recorded with the RETeval™ system under mydriatic-free conditions.

METHOD: This was a retrospective study of 82 eyes of 60 patients with cataracts and 52 eyes of 38 patients who were pseudophakic. Flicker ERGs were recorded with the RETeval™ system (LKC Technologies, Gaithersburg, MD) under mydriatic-free condition with skin electrodes. Flicker ERGs were elicited by white light delivered at a frequency of 28.3 Hz and intensity of 8 Td-s. The implicit times and amplitudes of the ERGs recorded from the Grade 2 cataract, Grade 3 cataract, and pseudophakic groups were compared.

RESULTS/CONCLUSION: The mean amplitude was significantly smaller in both cataract groups than the pseudophakic group (Grade 2 cataract vs pseudophakic group, $P < 0.0001$; Grade 3 cataract vs pseudophakic group, $P < 0.0001$; Grade 2 cataract vs Grade 3 cataract, $P = 0.027$).

The mean implicit times was significantly longer in both cataract groups than the pseudophakic group (Grade 2 cataract vs pseudophakic group, $P = 0.046$; Grade 3 cataract vs pseudophakic group, $P = 0.0004$; Grade 2 cataract vs Grade 3 cataract, $P = 0.0084$).

The results indicate that the presence of Grade 2 or more cataracts will affect both the amplitude and

the implicit time of the flicker ERGs. The presence of cataracts should be taken into consideration when interpreting the flicker ERG recorded with RETeval™.

Miura G. et al. Flicker electroretinograms recorded with mydriasis-free RETeval system before and after cataract surgery, 2017

PURPOSE: The purpose of this study is to compare the amplitudes and peak times of the flicker electroretinograms (ERGs) recorded before and after cataract surgery with the RETeval from eyes without dilation.

METHOD: Thirty-two eyes of 32 patients (77.3 ± 6.5 years) that had grade 2 Emery–Little nuclear or cortical cataract without any other abnormalities were studied. Flicker ERGs were recorded with the RETeval system under mydriatic-free conditions. Skin electrodes were used to pick-up the ERGs that were elicited by white light delivered at a rate of 28.3 Hz and intensity of 2, 8, and 32 Td-s. The amplitudes and peak times of the flicker ERGs before and after cataract surgery were compared.

SUMMARY/CONCLUSION: These results indicate that the presence of cataracts will affect both the amplitudes and the peak times of the flicker ERGs even if the cataract is mild.

The effect of lens opacity on the peak time decreased as strengthen the light intensity increased. The effect will be essentially eliminated when the stimulus intensity was equal to 32 Td-s.

Kato, K. et al. Case of Lens-Induced Uveitis Associated with Supernormal Flicker ERG Amplitudes after Cataract Surgery, 2020

PURPOSE: To report our findings in a case of lens fragment-induced uveitis associated with supernormal flicker electroretinograms (ERGs) twenty months after the cataract surgery.

METHODS: This is an observational case report. Full-field flicker ERGs were recorded with the RETeval system. Optical coherence tomography (OCT) and slit-lamp biomicroscopy were used to assess the uveitis during the follow-up period.

RESULTS/CONCLUSION: A 70-year-old man, who had undergone cataract surgery 20 months earlier, visited our hospital with a complaint of decreased vision in his right eye. Slit-lamp biomicroscopy revealed corneal edema and a lens fragment was detected in the inferior part of the anterior chamber. OCT showed cystoid macular edema, and flicker ERGs showed a marked increase in the amplitude and a delay in the implicit time in the right eye. These abnormalities of the flicker ERGs improved gradually after the removal of lens fragment and application of topical anti-inflammatory medications.

Our case of lens-induced uveitis had supernormal flicker ERG amplitudes. Clinicians should be aware that eyes with uveitis can have larger-than-normal ERG amplitudes.

Tanikawa, A.et al. The Influence of Mild Cataract on ISCEV Standard Electroretinogram Recorded from Mydriatic Eyes, 2020

PURPOSE: To investigate the effect of mild cataract and its surgery on the ISCEV standard electroretinogram (ERG) by comparing pre- and postoperative ERGs elicited from fully dilated eyes.

METHODS: Twenty-two patients participated. Each eye had cataract of grade 2 according to Emery-Little classification. None had complications during and after phacoemulsification and intraocular lens implantation. According to the ISCEV standard, pre- and 1-week postoperative full-field ERGs, dark adapted (DA) 0.01, DA 3, DA 3 oscillatory potentials (OPs), DA 10, and light adapted (LA) 3, and LA 3 flicker, were elicited from fully dilated eyes using skin electrodes. Photopic negative response (PhNR) 1 amplitude was measured from the baseline to the trough before the i-wave in the LA 3 ERG waveform. Statistical analysis was performed using SigmaPlot version 11.0 (Systat Software, Inc., San Jose, CA, USA). Pre- and postoperative data were compared using a paired t-test. Non-normally distributed data were evaluated using the Wilcoxon signed rank test.

RESULTS/CONCLUSION: The pre- and 1-week postoperative amplitudes in each component were as follows: [...], a-wave of LA 3: 7.2 ± 2.6 μV and 8.2 ± 2.2 μV ($p = 0.025$), b-wave of LA 3: 30.6 ± 12.9 μV and 35.3 ± 12.7 μV ($p = 0.003$), PhNR1: 5.8 ± 2.5 μV and 5.5 ± 2.6 μV ($p = 0.562$), and LA 3 flicker: 25.4 ± 8.9 μV and 27.8 ± 8.6 μV ($p = 0.039$), respectively. The implicit time of all the components did not reveal significant differences before and after surgery.

Surgical

Ozaki K. et al. Electroretinograms recorded with skin electrodes in silicone oil-filled eyes, 2019

PURPOSE: To assess the physiology of the retina by electroretinography (ERG) with skin electrodes in eyes that had undergone vitrectomy with silicone oil (SO) tamponade.
METHOD: ERGs were recorded from eleven eyes with complex vitreoretinal disorders and from the normal fellow eyes. The affected eyes underwent pars plana vitrectomy (PPV) with SO tamponade. ERGs were recorded before and after the SO was removed. The amplitudes and implicit times of the a- and b-waves of the affected eyes were compared to those of the normal fellow eyes. In addition, the ratios of the amplitudes of the b-waves of the affected eyes to those of the fellow eyes were compared before and after the SO was removed.
The RETeval system (LKC Technologies Inc., Gaithersburg, MD; (…)) is a handheld, portable ERG device that uses skin electrodes to pick up the ERGs. The recordings can be done rapidly, and the skin electrodes reduce the risk of corneal abrasion and infections. Thus, it allows clinicians to assess the physiology of the retina shortly after any type of intraocular surgery. These properties prompted us to evaluate the retinal function by the RETeval system in eyes filled with SO before and after the silicone oil was removed. The relationships of the ERG findings to the clinical conditions were determined.
RESULTS/ CONCLUSION: ERGs were recordable from 7 eyes (63.6%) before the SO was removed and 11 eyes (100%) after the SO was removed. The a- and b-wave amplitudes were significantly smaller in the affected eyes than those of the fellow eyes at the baseline. The b-wave amplitude before the removal of the SO was significantly and positively correlated with that after the SO removal. The ratios of the b-waves of the affected/normal fellow eye significantly increased after the SO was removed.
The results indicate that ERGs picked up by skin electrode can be used to assess the physiology of the retina in eyes with a SO tamponade. The amplitude of the b-waves of the ERGs in silicone-filled eyes can be used to predict the amplitude after the silicone is removed.

Shibuya M. et al. Electroretinographic recordings with skin electrodes to assess effects of vitrectomy gas tamponade on eyes with rhegmatogenous retinal detachment, 2019

PURPOSE: The purpose of this study was to evaluate the retinal function by electroretinograms (ERGs) recorded with the RETeval system using skin electrodes after pars plana vitrectomy (PPV) with gas tamponade in eyes with a rhegmatogeneous retinal detachment (RRD).
METHOD: Flicker ERGs were recorded from 17 eyes with an RRD before (baseline), within 2 weeks after the PPV when the size of the tamponade gas was approximately one-half of the vitreous cavity (P1), and when the gas had been completely absorbed (P2). The amplitudes of the flicker ERGs at each phase were compared to that at the baseline.
RESULTS/ CONCLUSION: We conclude that recordings the flicker ERGs with skin electrodes can be used to assess the physiology of eyes even with the vitreous cavity half-filled with the gas used to tamponade the retina.
Because ERG recordings takes only a few minutes, we believe that it is practical for the clinical use to obtain clinically relevant information.
Another of our significant findings was that the amplitudes of the flicker ERGs at Phase 1 were positively and significantly correlated with the amplitudes at Phase 2.
In conclusion, our results indicate that skin electrodes with the RETeval system can be used to assess the physiological status eyes half-filled with SF6 gas. The findings can provide information on the degree of recovery of the retina a short time after the PPV. This is significant because the amplitudes of the ERGs at Phase 1 were significantly correlated with the ERGs at Phase 2.

Wang, KJ. Electrophysiology as a prognostic indicator of visual recovery in diabetic patients undergoing cataract surgery, 2021

PURPOSE: Visual outcomes after cataract surgery in diabetic patients with retinal or visual pathway disease are difficult to predict as the fundus may be obscured, and assessment of visual potential is challenging. This study assessed the value of visual electrophysiology as a prognostic indicator of visual recovery in diabetic patients with cataract, prior to cataract surgery.

METHODS: Forty-one diabetic patients (aged 52–80; 74 eyes) and 13 age-matched non-diabetic control patients (21 eyes) were examined prior to cataract surgery. Pre-surgical examinations included best-corrected visual acuity (BCVA), slit-lamp bio-microscopy, ISCEV-standard full-field electroretinography (ffERG), and flash visual evoked potential (flash VEP) testing. Electrophysiological assessments included quantification of the DA and LA ERG, oscillatory potentials (OPs; OP1, OP2, OP3, OP4) and flash VEP P1, P2, and P3 components. Post-operative BCVA was measured in all cases and the diabetic patients grouped according to the severity of visual acuity loss: mild (logMAR ≤ 0.1), moderate (0.1 < logMAR < 0.5), or severe (logMAR ≥ 0.5). A fourth group included those without diabetes. The pre-surgical electrophysiological data was compared between the four groups by analysis of variance.

RESULTS: The severity of post-surgical visual acuity loss in the diabetic patients was classified as mild (N=22 eyes), moderate (N=31 eyes), or severe (N=21 eyes). In the group without diabetes, post-surgical visual impairment was classified as mild (N=21 eyes). The pre-operative DA 10.0 ERG a-wave amplitudes, DA 3.0 ERG OP2 amplitudes, and the LA 3.0 a- and b-wave amplitudes showed best significant differences among the four groups. The flash VEP did not show significant difference between groups.

CONCLUSION: Electrophysiological assessment of diabetic patients with cataract can provide a useful measure of retinal function. Full-field ERG components, including the DA 10.0 ERG a-wave, DA 3.0 ERG OP2 component, and the LA 3.0 a- and b-wave amplitudes, are of prognostic value in predicting post-surgical visual acuity, and may inform the surgical management of cataract patients with diabetes.

Kato, K. Transient Increase of Flicker Electroretinography Amplitudes after Cataract Surgery: Association with Postoperative Inflammation, 2023

PURPOSE: To determine the characteristics and cause of the increase in the amplitude of flicker electroretinography (ERG) after cataract surgery.

DESIGN: Prospective, observational clinical study. Participants: Thirty patients who underwent cataract surgery.

Methods: Flicker ERGs were recorded with the RETeval system without mydriasis. The central macular thickness (CMT) was measured by OCT and the aqueous flare value (AFV) by laser flare-cell photometry. These examinations were performed before surgery and 1 day, 1 week, 1 month, 2 months, and 3 months after surgery. Linear regression analysis through the origin was used to compare the correlations between the relative changes in flicker ERG amplitudes and the changes in the CMT and AFV at different times after the surgery.

MAIN OUTCOME MEASURES: The amplitude of flicker ERGs, CMT, and AFV.

RESULTS: The mean amplitude of flicker ERGs increased significantly by 31% at 1 week after surgery ($P < 0.001$); a significant increase in the amplitudes was not present at 3 months after the surgery. The mean AFV was significantly increased at 1 day after surgery ($P < 0.001$), and the CMT was significantly increased at 1 to 3 months after surgery ($P < 0.001$). The changes in flicker ERG amplitudes at 1 week after surgery were significantly associated with the changes in the CMT at 1 to 3 months after surgery ($P < 0.05$), and they were weakly associated with the changes in AFV at 1 day after surgery (P ¼ 0.05).

CONCLUSIONS: These results suggest that the increase in the amplitude of flicker ERGs after cataract surgery is a transient phenomenon that has a peak at 1 week after surgery. The increase of flicker ERG amplitude was associated with measures that are frequently used to evaluate postoperative inflammation.

Sakata, K. Electroretinographic Evaluations Using Skin Electrode of Eyes with Bleb-Related Endophthalmitis Following Vitrectomy with 0.025% Povidone Iodine Irrigation, 2024

PURPOSE: To determine whether 0.025% povidone-iodine (0.025% PI) in the irrigation solution during vitrectomy for endophthalmitis is safe.

METHODS: Two cases of bleb-associated endophthalmitis were treated with vitrectomy using 0.025% PI in the irrigation solution. The RETevel electroretinographic (ERG) system with skin electrodes was used to assess the physiology of the retina pre- and postoperatively.

CASE: Case 1 was a 46-year-old man who had atopic keratoconjunctivitis and underwent trabeculectomy with the creation of a bleb after there was a rise in the intraocular pressure. One month postoperatively, a mild filtering bleb-associated endophthalmitis developed, and the eye was treated with intravitreal and subconjunctival injections of vancomycin (VCM) and ceftazidime (CAZ). After three days, the fundus was not visible and B-mode echography showed an area of high brightness in the retina. Vitrectomy with irrigation with VCM and CAZ, and 0.025% PI was performed successfully. Pre- and postoperative ERGs showed an improvement in both the a- and b-wave amplitudes and the b/a ratio was stable at 2.0. Case 2 was a 63-year-old man who had undergone trabeculectomy for glaucoma. Five years later, the eye developed blebitis which was treated with topical and subconjunctival injections of VCM and CAZ. Three days later, vitreous opacities appeared and a high brightness area was seen in the B-mode echographic images. Vitrectomy with VCM and CAZ, and 0.025% PI irrigation was successfully performed. Comparisons of the pre- and postoperative ERGs found that the a- and b- wave amplitudes of the ERGs increased and the b/a ratio was stable at approximately 1.5.

CONCLUSION: Vitrectomy with 0.025% PI irrigation is safe and ERG recordings with skin electrodes can be used to evaluate the preand postoperative retinal physiology safely.

PLAIN LANGUAGE SUMMARY: We report our findings in two cases of bleb-related endophthalmitis that underwent pars plana vitrectomy (PPV) with irrigation with 0.025% povidone-iodine (PI)-Balanced Salt Solution (BSS) PLUS (Alcon Laboratories, Fort Worth, TX). The retinal function was evaluated by full-field electroretinograms (ERGs)

recorded with skin electrodes before and after the vitrectomy. At present, there is no consensus on whether patients with bleb-related endophthalmitis should be treated with PPV or treated solely by intravitreal antibiotics. It was recently reported that vitrectomy using an irrigation solution containing 0.025% PI followed by postoperative antibiotics was effective and safe for the treatment of endogenous endophthalmitis and postoperative endophthalmitis. However, iodine is known to be retinotoxic depending on its concentration. Electroretinography is a useful method to evaluate the safety of medications because it represents the physiology of the entire retina. However, conventional recording procedures with contact lens electrodes cannot be used in eyes with bleb associated endophthalmitis. Therefore, we performed ERG using skin electrodes which were introduced relatively recently. As a result, electroretinographic response showed that retinal function was not altered after surgery in these two cases.

Kashima, Y. Transient increase of flicker electroretinograms after combined cataract surgery and vitrectomy for idiopathic epiretinal membrane, 2024

To determine the characteristics of the changes in the amplitude of the flicker electroretinograms (ERGs) after combined cataract surgery and vitrectomy for an idiopathic epiretinal membrane (ERM). To accomplish this, we conducted a prospective study on 20 patients. Flicker ERGs and central macular thickness (CMT) were measured before the surgery (baseline), and at 1 week, 1 month, 3 months, and 6 months postoperatively. The mean amplitude of the flicker ERGs increased significantly by 63.5% at 1 week after surgery ($P < 0.001$) and then gradually decreased. The amplitude at 6 months was not significantly different from the baseline amplitude. This transient increase in the flicker ERG amplitudes after ERM surgery suggests that electrophysiologic evaluations of the therapeutic effects of vitrectomy should be performed 6 months postoperatively. The mean CMT decreased significantly at 1 week postoperatively ($P < 0.001$) and continued to decrease progressively over six months. The relative increase of amplitude at 1 week was significantly associated with the relative decrease of CMT at 6 months, and evaluation of retinal functional changes at 1 week may be able to predict the postoperative course of the ERM.

Kumagai, T. et al. Electroretinograms before and after extraction of large intraocular iron foreign body, 2019

PURPOSE: We present our findings in a case with an intraocular foreign body in which the electroretinographic (ERG) findings were useful.

METHOD: Preoperative ERGs with a contact lens electrode showed reduced responses with many blinking artifacts. Lensectomy and pars plana vitrectomy were performed and a fragment of a wire brush was seen embedded in the superior nasal retina which was removed. The decimal visual acuity improved to 1.2 two weeks later. The postoperative ERG performed with a skin electrode showed reduced responses in the injured eye.

RESULTS/CONCLUSION: We recommend that the physiology of the retina to be assessed by recording ERGs with a skin-type electrode as soon as possible after a traumatic injury to the eye.

Urrea-Victoria, T. Postoperative Multimodal Analysis in Successful Gas Displacement of a Submacular Hemorrhage, 2021

In this report, we describe a case of timely gas vitrectomy to displace a moderate submacular hemorrhage from the submacular space without tPA, release vitreoretinal traction along the borders of a posterior retinal tear, and analyze postoperative multimodal imaging findings in a 34-year-old male patient whose right eye was injured by a stone. The patient underwent a successful nontissue plasminogen activator gas vitrectomy 3 days after the accident. A multimodal evaluation with spectral-domain optical coherence tomography (SD-OCT), 10-2 and 30-2 campimetry, microperimetry, multifocal electroretinography (mfERG), and visual evoked potentials was performed 6 months after the accident. The multimodal imaging tests yielded abnormal foveal SD-OCT patterns, with a fibrous sealed tear in the retinal pigment epithelium. Campimetry showed low levels of retinal sensitivity; microperimetry and mfERG revealed a subnormal retinal response and a reduction in the N1 and P1 wave amplitudes. The visual evoked potential responses were normal. Multidisciplinary examination at 6 months postoperatively revealed a structurally and functionally abnormal macula. The retina remained attached. Our functional findings indicate that submacular hemorrhage should be treated in a timely manner to minimize photoreceptor damage.

Górska, A. Assessment of Retinal Function Using Full-Field Electroretinography in Patients Undergoing Vitrectomy for a Macular Hole, 2025

PURPOSE: The aim of this study was to evaluate retinal function before and after vitrectomy in patients with a fullthickness macular hole (FTMH).

METHODS: A total of 48 patients with FTMHs confirmed by spectral-domain optical coherence tomography (OCT) were enrolled. All underwent 23-gauge pars plana vitrectomy (PPV) with internal limiting membrane (ILM) peeling and gas tamponade. Retinal function was assessed using the RETevalTM (LKC Technologies, Inc., Germantown, MD) device before surgery and at one, three, six, and 12 months postoperatively. Electroretinography (ERG) recordings included standard photopic responses, photopic negative response (PhNR), and ON-OFF responses. Anatomical outcomes were evaluated using OCT.
RESULTS: Statistical analysis was completed for 48 patients. Postoperative anatomical closure of the macular hole was achieved in all cases. A significant improvement was observed in both distances best corrected visual acuity (DBCVA) and near best corrected visual acuity (NBCVA) of the affected eye after surgery compared to preoperative values ($p < 0.001$). No significant differences were found between the ERG parameters of the affected eye and the healthy eye examined before surgery. Postoperatively, several photopic ERG implicit times (ITs) were prolonged in the operated eyes compared with the fellow eyes.
CONCLUSIONS: The RETevalTM system provides a non-invasive, standardized means of monitoring retinal function in patients with FTMHs undergoing vitrectomy. An FTMH appears to be a localized phenomenon, not associated with significant functional impairment of the entire retina, as evidenced by the lack of statistically significant differences in preoperative ERG parameters between the affected and fellow healthy eyes.

Ichinohe, H. Electroretinography (ERG) alterations following positional changes in gas-filled eyes after a vitrectomy, 2026

PURPOSE: Recording electroretinograms (ERGs) in eyes with intraocular gas tamponade is difficult, and the mechanism remains unclear. We evaluated the effect of intraocular gas on ERGs by comparing recordings at different body positions.

METHODS This study included 31 patients who underwent vitrectomy with sulfur hexafluoride (SF6) or air tamponade at Hirosaki University (between May 2023 and October 2024). The patients included those with retinal detachment (25 patients), macular holes (4 patients), and epiretinal membranes (2 patients). ERGs were recorded using skin electrodes when approximately 50% of the vitreous cavity was filled with the intraocular gas. ERGs were recorded in sitting, supine, and face-down positions. Amplitudes and latencies of the LA 3 b-wave and LA 30 Hz were compared using the Wilcoxon signed-rank and Friedman tests.

RESULTS In the gas-filled eyes, amplitudes in the face-down position were smaller, and latencies were longer than those in the other positions ($p < 0.05$). Median amplitudes in the gas-filled eyes in the sitting, supine, and face-down positions were 20.4, 19.5, and 10.1 μV for LA 3 and 14.4, 15.5, and 7.11 for LA 30 Hz, respectively; median latencies were 32.5, 33.0, and 34.3 ms for LA 3 and 30.8, 30.0, and 34.3 for LA 30 Hz, respectively.

CONCLUSIONS ERG amplitudes were reduced and latencies were prolonged in the face-down position, which may be attributed to a larger retinal area being covered by intraocular gas. The gas acts as an insulator, and the gas-covered retina may not effectively generate or transmit electrical signals.

Im, S. Correlation Between Portable Photopic Electroretinography and Postoperative Best-Corrected Visual Acuity in Patients with Diabetic Vitreous Hemorrhage, 2026

PURPOSE: To determine the correlation between electroretinography (ERG) performed using a handheld ERG device equipped with skin electrodes and postoperative best-corrected visual acuity (BCVA) in patients with vitreous hemorrhage (VH) due to proliferative diabetic retinopathy (PDR).
METHODS: The medical records of patients who underwent vitrectomy for diabetic vitreous hemorrhage (DVH) caused by PDR at our institution between July 1, 2017, and June 30, 2023, were reviewed retrospectively. We analyzed the correlation between preoperative ERG obtained using a handheld ERG device RETevalTM (LKC Technologies, Gaithersburg, MD, USA), RETevalTM skin electrodes (Sensor strips, LKC Technologies, Gaithersburg, MD, USA), and postoperative BCVA.
RESULTS: We evaluated the medical records of 70 eyes of 70 patients. The BCVA, which was measured in logarithm of the minimal angle of resolution (logMAR) units, improved from 1.91±0.504 preoperatively to 0.287±0.225 postoperatively ($p<0.001$). In the group that underwent panretinal photocoagulation before VH, the amplitudes of the b-wave in photopic ERG and 30-Hz flicker ERG were negatively correlated with the postoperative BCVA. The implicit times of the b-wave in photopic ERG and 30-Hz flicker ERG were positively correlated with the postoperative BCVA ($p<0.05$).
CONCLUSIONS: Photopic ERG recorded using a handheld retinal ERG device equipped with skin electrodes can aid in predicting the visual prognosis in patients with severe VH caused by diabetes mellitus.

Other Indications

Hayashi Y. Case of convulsive seizure developing during electroretinographic recordings: a case report, 2018

BACKGROUND: To present our findings in a case of convulsive seizures and loss of consciousness that developed during recording electroretinograms (ERG).

CASE PRESENTATION: A 34-year-old man had reduced vision in his left eye for about 15 years, and night blindness for about two years. His visual acuity was 20/15 in the right eye and 20/50 in the left eye. The fundus was normal but the sensitivity in the macular region of the left eye was decreased. Optical coherence tomography (OCT) showed partial loss of the interdigitation zone. Upon completion of the flicker ERG recording, a paralysis developed in both upper limbs, then convulsions of the lower limbs followed by a loss of consciousness. The convulsions disappeared after an intravenous injection of diazepam. After that incident, he reported that he had had previous conscious-loss seizures.

CONCLUSIONS: Photosensitive epileptic seizures can occur with the light stimuli used for conventional ERG recordings. We recommended that clinicians request information on any prior seizure episodes of the patients and their family members before ERG recordings.

Sekaran A. et al. Creating a Health Utility Value for Birdshot Chorioretinopathy, 2020

PURPOSE: To create a health utility value for birdshot chorioretinopathy (BCR) using Time Trade-Off (TTO) and Standard Gamble (SG) utilities.
METHOD: Adult BCR patients completed TTO, SG, EQ-5D-5L, and NEI VFQ-25 questionnaires and underwent a detailed history and clinical examination.
RESULTS: A total of 28 BCR patients (9 M, 19 F; mean age 62 years, range 47–83) were included. There were 22 patients with a logMAR vision of 0.3 or better in both eyes. Mean TTO was 0.90 ± SD 0.18 (range 0.33–1.0) and mean SG was 0.94 ± SD 0.14 (range 0.5–1.0). TTO correlated with EQ-5D-5L index value (p = .024) and NEI VFQ-25 composite score (p = .015).
CONCLUSIONS: Of 28 patients with BCR, 11 would trade remaining life (mean 5.4 years), and 6 would take a risk of immediate death (mean 28% risk), in return for perfect vision in both eyes for the rest of their life.

Enomoto, H. et al. Case with Metastatic Cutaneous Malignant Melanoma That Developed Vogt–Koyanagi–Harada-like Uveitis Following Pembrolizumab Treatment, 2021

PURPOSE: The study reports a case with metastatic cutaneous malignant melanoma that developed Vogt–Koyanagi–Harada-like uveitis during pembrolizumab treatment.

METHOD: 68-year-old women presented with blurred vision in both eyes 3 months after beginning pembrolizumab adjuvant therapy for a malignant melanoma on the lower thigh. Optical coherence tomography showed a serous retinal detachment (SRD) in the right eye and marked choroidal thickening in both eyes. Fluorescein angiography showed spotted hyperfluorescence in the right eye and leakage of fluorescein from both optic disks. Indocyanine green angiography showed dark hypofluorescent spots in both eyes. She was diagnosed with Vogt–Koyanagi–Harada-like uveitis induced by pembrolizumab and discontinued the pembrolizumab. She was then treated with oral prednisolone and topical betamethasone. One week later, the symptoms were improved, and 1 month later the choroidal thickening in both. eyes and the SRD of the right eye were not present. The implicit time of the full-field flicker ERGs recorded by RETeval system was significantly delayed at the initial examination but improved within a few weeks after the steroid replacement treatment.

RESULTS/CONCLUSION: Our case with Vogt–Koyanagi–Harada like uveitis induced by pembrolizumab had a reduction in the degree of uveitis after discontinuation of the pembrolizumab and use of oral prednisolone and topical betamethasone. Flicker ERGs were helpful in monitoring the retinal function before and after the steroid treatment.

Raharja, A. Exploratory Study of the Association between the Severity of Idiopathic Intracranial Hypertension and Electroretinogram Photopic Negative Response Amplitude Obtained Using a Handheld Device, 2021

PURPOSE: The photopic negative response (PhNR) is a negative component of the photopic flash electroretinogram that follows the b-wave and is thought to arise from the retinal ganglion cells. Reduction in its amplitude in idiopathic intracranial hypertension (IIH) has been previously documented using formal electroretinography.

METHODS: This study explored the use of a handheld device (RETeval, LKC technologies, Gaithersburg, MD, USA) in 72 IIH patients of varying stages and severity (and seven controls) and investigated associations between PhNR parameters and disease severity.

RESULTS: PhNR amplitudes at 72 ms (P72) and p-ratio (ratio to b-wave peak value) differed significantly across groups, with a trend towards smaller amplitudes in those with severe IIH, defined as papilloedema with Modified Frisén Scale (MFS) ≥ 3, retinal nerve fibre layer (RNFL) ≥ 150 µm or atrophic papilloedema ($p = 0.0048$ and $p = 0.018$ for P72 and p-ratio, respectively). PhNR parameters did not correlate with MFS, RNFL thickness, standard automated perimetry mean deviation or macular ganglion cell layer volume.

CONCLUSION: This study suggests that PhNR measurement using a handheld device is feasible and could potentially augment the assessment of disease severity in IIH. The clinical utility of PhNR monitoring in IIH patients requires further investigation.

Han, KJ. Using RETeval System Flicker Electroretinography for Evaluation of Dense Vitreous Hemorrhage, 2021

PURPOSE: To determine whether the RETeval electroretinography (ERG) system can be used to evaluate eyes with dense vitreous hemorrhage (VH).

METHODS: This retrospective case series study included 69 eyes of 69 patients with acute dense VH. Flicker ERGs were recorded by the RETeval system, an ERG device with adhesive skin electrodes. We evaluated the flicker ERG amplitudes in eyes with VH and the ratio of the VH eye amplitudes compared to the fellow eye amplitudes for each VH cause.

RESULTS: In patients with rhegmatogenous retinal detachment (RRD), the amplitude ratios were extremely low (0.08 ± 0.03). To detect RRD, the area under the receiver operating characteristic curve was 0.977 (95% confidence interval, 0.943–1.000) (best RRD cut off value, 0.14; sensitivity, 100.0%; specificity, 95.4%). The flicker ERG amplitude was not significantly correlated with initial visual acuity ($\rho = -0.189$, $P = .120$) but was positively correlated with postoperative visual acuity in eyes with VH ($\rho = -0.328$, $P = .006$).

CONCLUSION: The RETeval ERG system was found to be a useful diagnostic option in situations where dense VH precluded fundus examination or posterior vitreous detachment was indistinguishable from RRD.

Shinohara, Y. Clinical Findings of Melanoma-Associated Retinopathy with antiTRPM1 Antibody, 2021

INTRODUCTION. We report the clinical features and clinical course of melanoma-associated retinopathy (MAR), in which autoantibodies against the transient receptor potential cation channel subfamily M member 1 (TRPM1) were detected.

CASE PRESENTATION. A 74-year-old man was referred to our hospital for treatment of bilateral vision loss. The best-corrected visual acuity was 20/100 in the right eye and 20/200 in the left eye. His electroretinogram (ERG) showed a reduced b-wave and a normal dark-adapted a-wave in both eyes. Optical coherence tomography (OCT) revealed loss of the interdigitation zone in both eyes. We strongly suspected MAR based on the markedly reduced b-wave in the ERG and a history of intranasal melanoma. The diagnosis was confirmed after autoantibodies against TRPM1 were detected in his blood serum. Fifteen months later, his ERG remained unchanged, and OCT showed bilateral cystic changes in the internal nuclear layer. The visual acuity in both eyes also remained unchanged.

CONCLUSIONS. Anti-TRPM1 autoantibodies were detected in a patient diagnosed with MAR who had negative flash ERG and retinal microstructural abnormalities, and the impairment did not recover during the follow-up period. Identification of anti-TRPM1 antibodies was helpful in confirming the diagnosis of MAR.

Wang Q. Whole-Exome Sequencing and Copy Number Analysis in a Patient with Warburg Micro Syndrome, 2022

Warburg Micro syndrome (WARBM) is an autosomal recessive neuro-ophthalmologic syndrome characterized by microcephaly, microphthalmia, congenital cataracts, cortical dysplasia, corpus callosum hypoplasia, spasticity, and hypogonadism. WARBM is divided into four subtypes according to the causative genes, of which RAB3GAP1 (OMIM# 602536) accounts for the highest proportion. We collected detailed medical records and performed whole-exome sequencing (WES) for a congenital cataract patient. A novel heterozygous frameshift RAB3GAP1 variant was detected in a boy with a rare ocular phenotype of bilateral membranous cataracts accompanied by a persistent papillary membrane. Further copy number variation (CNV) analysis identified a novel deletion on chromosome 2q21.3 that removed 4 of the 24 exons of RAB3GAP1. The patient was diagnosed with WARBM following genetic testing. The present study expands the genotypic and phenotypic spectrum of WARBM. It suggests applying whole exome sequencing (WES) and CNV analysis for the early diagnosis of syndromic diseases in children with congenital cataracts.

Perche O. Large-conductance calcium-activated potassium channel haploinsufficiency leads to sensory deficits in the visual system: a case report, 2022

Background: Mutations in the genes encoding the large-conductance calcium-activated potassium channel, especially KCNMA1 encoding its α-subunit, have been linked to several neurological features, including intellectual disability or autism. Associated with neurodevelopmental phenotypes, sensory function disturbances are considered to be important clinical features contributing to a variety of behavioral impairments. Large-conductance calcium-activated potassium channels are important in regulating neurotransmission in sensory circuits, including visual pathways. Deficits in visual function can contribute substantially to poor quality of life, while therapeutic approaches aimed at addressing such visual deficits represent opportunities to improve neurocognitive and neurobehavioral outcomes.
Case presentation: We describe the case of a 25-year-old Caucasian male with autism spectrum disorder and severe intellectual disability presenting large-conductance calcium-activated potassium channel haploinsufficiency due to a de novo balanced translocation (46, XY, t [9; 10] [q23;q22]) disrupting the KCNMA1 gene. The visual processing pathway of the subject was evaluated using both electroretinography and visual contrast sensitivity, indicating that both retinal bipolar cell function and contrast discrimination performance were reduced by approximately 60% compared with normative control values. These findings imply a direct link between KCNMA1 gene disruption and visual dysfunction in humans. In addition, the subject reported photophobia but did not exhibit strabismus, nystagmus, or other visual findings on physical examination.
Conclusions: This case study of a subject with large-conductance calcium-activated potassium channel haploinsufficiency and photophobia revealed a visual pathway deficit at least at the retinal level, with diminished retinal light capture likely due to bipolar cell dysfunction and an associated loss of contrast sensitivity. The data suggest that large-conductance calcium-activated potassium channels play an important role in the normal functioning of the visual pathway in humans, and that their disruption may play a role in visual and other sensory system symptomatology in large-conductance calcium-activated potassium channelopathies or conditions where disruption of large-conductance calcium-activated potassium channel function is a relevant feature of the pathophysiology, such as fragile X syndrome. This work suggests that the combined use of physiological (electroretinography) and functional (contrast sensitivity) approaches may have utility as a biomarker strategy for identifying and characterizing visual processing deficits in individuals with large-conductance calcium-activated potassium channelopathy.

Makita, K. Electroretinographic and Optical Coherence Tomographic Evaluations of Eyes with Vitreoretinal Lymphoma, 2023

Vitreoretinal lymphomas (VRLs) present with different clinical characteristics. However, only a few case reports have been published that evaluated the retinal function and the retinal morphology. The relationship between retinal morphology and function of eyes with a vitreoretinal lymphoma (VRL) was investigated via optical coherence tomography (OCT) and electroretinography (ERG). The ERG and OCT findings in 11 eyes of 11 patients (69.4 ± 11.5 years old) who were diagnosed with VRL at the Saitama Medical University Hospital between December 2016 to May 2022 were studied. The decimal best-corrected visual acuity ranged from hand movements to 1.2 (median 0.2). Histopathological studies of the vitreous specimens showed class II VRL in one eye, class III VRL in seven eyes, class IV VRL in two eyes, and class V VRL in one eye. The IgH gene rearrangement was positive in three of the six eyes tested. The OCT images showed morphological abnormalities in 10 of the 11 (90.9%) eyes. Severe attenuation was found for the amplitudes of the b-wave of the DA 0.01 ERG in 6 of 11 eyes (54.5%), the DA 3.0 a-wave in 5 of 11 eyes (45.5%), the DA 3.0 b-wave in 36.4%, the LA 3.0 a-wave in 36.4%, the LA 3.0 b-wave in 18.2%, and flicker responses in 36.4% of the eyes. None of the DA 3.0 ERGs had a negative shape (b/a < 1.0). In the five eyes in which the a-wave was severely attenuated, hyperreflective dots were observed subretinally. The ERG analysis in eyes with a VRL indicates a relatively severe dysfunction of the outer retinal layer and was helpful in determining the site of the morphological changes in eyes with VRL.

Yamada, F. Case of persistent corneal epithelial damage after cataract surgery leading to diagnosis of vitamin A deficiency, 2024

PURPOSE: To report our findings of reduced full-field electroretinograms (ff-ERGs) and abnormal optical coherence tomographic (OCT) images in a patient with poor visual acuity after cataract surgery who was eventually diagnosed with vitamin A deficiency (VAD).

METHODS: This was a clinical study of a patient who complained of blurred vision after cataract surgery. To determine the cause of the reduced vision, we recorded full-field electroretinograms (ff-ERGs) to determine the scotopic and photopic status of the retina. We also performed optical coherence tomography to assess the changes in the retinal structure. Serological tests were performed.

RESULTS: A 74-year-old man presented with persistent corneal epithelial damages and reduced vision that developed after conventional cataract surgery. OCT showed an interrupted ellipsoid zone, and fundus autofluorescence (FAF) showed a severe hypofluorescence in the retina of the left eye. The scotopic ff-ERGs were severely reduced, and the photopic ff-ERGs were mildly reduced. Serological examinations revealed a vitamin A

concentration < 7 IU/dL (normal, 97–316 IU/dL). Based on these findings, we diagnosed the patient with VAD and started treatment with oral vitamin A supplements. After three months, his visual acuity, ff-ERGs, and OCT findings recovered to normal levels. The amplitudes and implicit times of the RETeval flicker ERGs increased to be within the normal range, and the hypofluorescence of the left eye disappeared. The length of the photoreceptor outer segments increased after the vitamin A supplementation.

CONCLUSIONS: Our findings indicate that the ERGs are helpful for diagnosing patients with VAD associated with persistent corneal epithelial damages.

Inoue, S. Retinal dysfunction of syphilitic outer retinopathy, 2024

PURPOSE: We present our findings in two cases of retinal dysfunction caused by syphilitic outer retinopathy.

CASE 1: A 59-year-old man visited our clinic complaining of blurred vision in his left eye. Optical coherence tomography (OCT) demonstrated an absence of the ellipsoid zone (EZ) in the left eye. A round yellowish-white lesion was observed in the posterior pole of the left fundus. Fundus autofluorescence (FAF) showed hyperfluorescent areas in the posterior pole of both fundi although no specific ophthalmoscopic findings were seen in the right eye. The amplitudes of the LA 3.0 1 Hz and LA 3.0 30 Hz ERG responses were reduced with better preservation of the rod responses. Based on a strong positivity to the rapid plasma reagin (RPR) assay and the Treponema pallidum hemagglutination (TPHA) test, he was diagnosed with syphilitic outer retinopathy and treated with systemic antibiotics. The treatment resulted in a restoration of the retinal structures and cone function.

CASE 2: A 47-year-old man was referred to our clinic complaining of reduced vision in both eyes. Although the ocular fundus appeared normal, FAF showed a diffuse hyperfluorescent area in the posterior pole and multiple hyperfluorescent spots. Indocyanine green angiography showed multiple confluent areas of hypofluorescence. OCT demonstrated irregular EZs in both eyes. The amplitudes of the LA 3.0 1 Hz and LA 3.0 30 Hz ERG responses were slightly reduced with prolonged implicit times. These findings are comparable to the findings in patients with multiple evanescent white dot syndrome. However, the strong positivity to the RPR and TPHA tests led us to diagnose the patient with outer retinopathy caused by syphilis. Systemic administration of antibiotics resulted in the restoration of the retinal structures and retinal function.

CONCLUSIONS: Syphilitic outer retinopathy affected the retinal structures and function that can be restored by antibiotic treatments.

Sarnat-Kucharczyk, M. Significant improvement of ganglion cell complex in optical coherence tomography and photopic negative response in electroretinography after transsphenoidal resection of pituitary macroadenoma, 2024

NO ABSTRACT AVAILABLE.

Pituitary adenomas (PAs), also known as pituitary neuroendocrine tumours (PitNET), are usually benign tumours of the anterior lobe of the pituitary gland.

a 59-year-old male patient, a truck driver, was admitted to the endocrinology department due to hyponatraemia, diarrhoea, and vomiting. Magnetic resonance imaging (MRI) of the brain revealed a pituitary macroadenoma 20 × 20 × 18 mm.

Static visual field (Octopus, Haag-Streit, Switzerland) was not typical for pituitary macroadenoma pattern changes, such as bitemporal homonymous hemianopia in the visual field, because the relative scotomata were presented in both hemifields in both eyes.

Optical coherence tomography (OCT) revealed significant thickness loss of the ganglion cell complex (GCC) in the nasal hemi-macula in the RE and in the upper nasal sector in the LE. The retinal nerve fibre layer around the optic nerve head was normal in both eyes. Photopic electroretinography (ERG), (RETeval, LKC, USA) with sensor strips electrodes was performed. The photopic negative response (PhNR) was normal, while b-wave amplitude was decreased in both eyes

One month after the operation, distance and near visual acuity remained stable in both eyes, and kinetic visual field was normal. Significant improvement was noted in the static visual field of both eyes. The remarkable increase in GCC of the nasal hemi-macula in the RE and recovery to normal GCC in the LE was observed. Significant improvement of b-wave amplitude and PhNR was recorded

Shunichiro, T. Electroretinographic Evaluations of Eyes With Endophthalmitis, 2024

PURPOSE: To determine the physiological status of the retina of eyes with endophthalmitis by examining the electroretinograms (ERGs) recorded with a portable recording system and to determine whether the pretreatment ERG findings were correlated with the best-corrected visual acuity (BCVA) after the treatment.

METHODS: We examined the medical records of 118 eyes of 108 patients who were diagnosed and treated for infectious endophthalmitis at Saitama Medical University Hospital, Japan, between January 2015 to November 2022. Of these, we studied the 25 eyes of 21 patients who had been evaluated by electroretinography. In bilateral cases, one eye was analyzed. The eyes were classified into those with postoperative endophthalmitis (group S, n = 12) and those with endogenous endophthalmitis (group E, n = 9). Photopic and flicker ERGs were recorded with the RETeval system. The pretreatment clinical factors studied were the ERG components that might be correlated with the post-treatment BCVA.

RESULTS: Eyes in Group E with larger amplitude flicker ERGs (P = 0.0053, ρ =−0.8333) had better BCVA after treatment. In Group S, eyes with larger amplitude flicker ERGs (P = 0.0086, ρ =−0.7173), photopic a-waves (P = 0.0323, ρ = 0.6177), and photopic b-waves (P = 0.0055, ρ =−0.7443) had better BCVA after treatment.

CONCLUSIONS: Simple and rapid ERG evaluations under light-adapted condition are helpful in evaluating the pretreatment retinal function and to determine the visual prognosisineyeswithendophthalmitis. Translational Relevance: Simple and non-time-consuming ERG evaluations are helpful in evaluating the retinal function in eyes with endophthalmitis and predicting the visual prognosis.

Lee, C. Novel electroretinography devices to detect hydroxychloroquine retinopathy: study protocol for a diagnostic accuracy and feasibility study, 2024

PURPOSE: Annual screening for hydroxychloroquine (HCQ) retinopathy is recommended, and electroretinography (ERG) is considered a gold-standard test, but there are screening shortfalls and standard ERG is burdensome and has limited availability. Newer, portable ERG devices using skin-based electrodes may increase screening capacity but need validation. This study aims to determine initial device accuracies and feasibility of further research.

METHODS: Prospective diagnostic device accuracy and feasibility study comparing novel ERG devices to standard screening tests. Three groups of 35 participants on HCQ, categorised by HCQ retinopathy (definite, possible and no retinopathy), and 35 healthy control participants, recruited by consecutive sampling, will have full field and multifocal ERG index tests, delivered using skin-contact electrodes by two devices—RETEval full-field and UTAS multifocal ERG, both manufactured by LKC Technologies (Gaithersburg, Maryland, USA), compared with spectral-domain optical coherence tomography and autofluorescence reference tests graded by two masked, independent retinal specialists. Eligible HCQ participants will either have diagnosed HCQ retinopathy or be eligible for screening per UK guidelines. Healthy control participants will have no prior HCQ exposure and be of similar age and sex to HCQ participants. Primary outcome is device-specific sensitivity and specificity. Secondary outcomes include the effect of dilation on device outputs, analysis of discriminatory waveforms, device acceptability and recruitment rate. Safety outcomes include adverse and serious adverse events and device events.

Kato, K. Case of uveitis with increased electroretinographic amplitudes following Nivolumab and Ipilimumab administration for malignant melanoma, 2025

PURPOSE: To report our flicker electroretinographic (ERG) findings in a patient who developed uveitis after treatment with immune checkpoint inhibitors (ICIs) for a metastatic malignant melanoma.

METHODS: ERGs were used to monitor retinal physiology in a patient with ocular complications following systemic ICI administration. Flicker ERGs were recorded using the RETeval system before and after the ICI treatments.

RESULTS: A 45-year-old woman was referred to our ophthalmologic clinic for baseline evaluations prior to initiating nivolumab/ipilimumab therapy. The patient had no ocular or ERG abnormalities at the initial visit, but three weeks after starting nivolumab/ipilimumab, she developed conjunctival hyperemia and tearing. Slit-lamp examination showed anterior chamber inflammation, and the ERGs showed a 40% increase in the amplitude from the baseline. However, optical coherence tomography (OCT) did not show any abnormalities. The anterior segment inflammation and increased ERG amplitude resolved with topical betamethasone. The patient developed significant liver damage after the second administration of nivolumab/ipilimumab, and this therapy was discontinued. Two steroid pulse therapies were followed by tapered oral prednisolone. During the follow-up period, no significant abnormalities were observed in the visual acuity or OCT images, but the ERG amplitudes increased from the first to the eighth month after the liver damage was detected. Five years later, the ERGs and OCT findings were within the normal limits, but she had developed a sunset glow fundus in both eyes.

CONCLUSION: ERGs may be a useful objective test for posterior inflammation induced by administration of ICIs that is not evident in OCT images.

Kapoor, R. Coats like vitreoretinopathy in retinitis pigmentosa – Multimodal imaging and management, 2025

A 14-year-old boy presented with complaints of bilateral, gradual blurring of vision associated with nyctalopia for five years. His best-corrected visual acuity (BCVA) was 20/60 in the right eye (RE) and 20/50 in the left eye (LE). Fundus examination revealed arteriolar attenuation, yellow-white diffuse retinal pigment epithelial degeneration, and cystoid macular edema (CME) in both eyes. In addition to the features of RP, the LE showed yellowish preretinal and subretinal exudation with telangiectatic vessels in the superior quadrant from 12 to 1 o' clock anteriorly and temporal to the fovea, while the RE showed minimal exudation with a few telangiectatic vessels in the superior quadrant at 12 o' clock anteriorly and temporal to the fovea [Fig. 1]. Optical coherence tomography (OCT) of the macula in both eyes confirmed CME [Fig. 1]. A flash electroretinogram showed barely detectable scotopic and photopic responses in both eyes [Fig. 2]. Widefield OCT angiography (OCTA) confirmed the presence of abnormally branching dilated and telangiectatic vessels in the superficial capillary plexus of the superior quadrant in the LE, along with areas of capillary dropout [Fig. 3]. He was treated with clinical/OCTA-guided focal laser over the telangiectatic vessels and barrage laser around the exudation (power: 200 mw, duration: 35 ms, 30 spots in the RE and 60 spots in the LE). Additionally, he was started on topical dorzolamide 2%, twice daily. At 5 month follow-up, BCVA improved to 20/30 and 20/40, with resolved CME and resolving exudation [Fig. 1]. Studies have shown bilateral involvement in most cases of RP with Coats-like vitreoretinopathy, typically located in the inferotemporal quadrant, and managed with laser or cryotherapy.[1–4] Our case is unique due to the presence of exudation and telangiectatic vessels in the superior quadrant. Laser treatment prompted rapid CME resolution, indicating that it was secondary to Coats disease rather than purely degenerative CME associated with RP.

Sarnat-Kucharczyk, M. The Relationship Between the Ganglion Cell–Inner Plexiform Layer, Retinal Nerve Fiber Layer, and Photopic Negative Response in Newly Diagnosed Pituitary Macroadenoma: 12-Month Prospective Follow-Up Study, 2025

BACKGROUND/OBJECTIVES: This prospective study evaluates the relationship between the ganglion cell–inner plexiform layer (GCIPL), retinal nerve fiber layer (RNFL), and photopic negative response (PhNR) in patients with newly diagnosed pituitary macroadenomas over 12 months.

METHODS: A total of 40 patients (80 eyes) were included, divided into a treatment group of 27 patients (54 eyes), receiving pharmacological and/or surgical intervention, and an observation group of 13 patients (26 eyes), with non-functional pituitary adenomas (NFPAs) that did not require treatment.

RESULTS: Key findings indicate a significant improvement in best corrected visual acuity (BCVA) after 12 months in the treatment group ($p = 0.02$) and a significant reduction in RNFL thickness in multiple quadrants ($p < 0.01$). Moreover, PhNR amplitude and W-ratio significantly increased in the treatment group ($p < 0.0001$). In the observation group, only GCIPL Inferior ($p = 0.0470$) and PhNR W-ratio ($p = 0.0015$) showed significant differences. Between-group comparisons showed significant differences in RNFL Nasal quadrant at baseline ($p = 0.0017$) and after 12 months ($p = 0.0150$). PhNR amplitude and W-ratio also differed significantly between groups at 12 months ($p = 0.0012$ and $p = 0.0016$, respectively). Correlations between OCT and ERG parameters were weak at baseline and diminished over time.

CONCLUSIONS: These findings suggest that GCIPL, RNFL, and PhNR analyses may be useful for monitoring disease progression and guiding treatment decisions in patients with pituitary macroadenomas.

Yoshida, A. Bilateral multiple retinal pigment epithelial detachments, 2025

PURPOSE: To report a rare case of bilateral idiopathic multifocal retinal pigment epithelial detachments (imfPEDs) and to describe the long-term morphological and functional changes observed over a 16-year follow-up period.

METHODS: A 49-year-old woman was diagnosed with imfPEDs based on multimodal imaging, including optical coherence tomography (OCT), fluorescein angiography (FA), and fundus photography. Full-field electroretinograms (ffERGs) and multifocal ERGs (mfERGs) were recorded to assess retinal function. The patient voluntarily discontinued follow-up but returned 16 years later due to cataract progression. Retinal morphology and function were re-evaluated using comparable multimodal imaging and electrophysiological methods.

RESULTS: At the initial visit, multiple bilateral pigment epithelial detachments (PEDs) were identified. OCT showed hyporeflective, dome-shaped PEDs with smooth borders, and ERG responses were within normal limits. Sixteen years later, some PEDs had resolved, others had newly developed or fused, and geographic atrophy was observed, particularly in the peripheral retina. Fundus autofluorescence (FAF), performed in place of FA, revealed hyperautofluorescent PEDs and numerous peripheral hypofluorescent spots. ffERGs remained normal, while mfERGs

showed localized attenuation with relatively preserved macular function. These findings were consistent with large colloid drusen and cuticular drusen.

CONCLUSION: This case demonstrates the slow morphological progression and relative functional preservation in bilateral imfPEDs over 16 years. Comparable multimodal imaging and electrophysiological testing were valuable in monitoring the long-term clinical course and support the classification of this phenotype as a variant of large colloid or cuticular drusen.

Fukuyama, S. Electroretinogram as an Early Diagnostic Biomarker for Acute Retinal Necrosis: A Multicenter Comparative Study, 2025

PURPOSE: Acute retinal necrosis (ARN) is a rare but severe ocular condition that often results in significant visual impairment or blindness. We aimed to determine whether ARN exhibits a distinct electroretinogram (ERG) waveform compared with other infectious and non-infectious uveitis forms.

METHODS: This retrospective observational multicenter study included a total of 73 patients; 21 with ARN, 9 with bacterial endophthalmitis, 16 with other types of infectious uveitis, and 27 with non-infectious uveitis. Full-field electroretinography was performed at the initial examination to evaluate retinal function. Additionally, initial and post-treatment visual acuity were recorded. The a- and b-wave amplitudes were measured and compared between the groups.

RESULTS: Patients with ARN had significantly reduced a- and b-wave amplitudes than the other types of infectious and non-infectious uveitis at the first visit ($p < 0.01$). Receiver operating characteristic analysis showed that an a-wave amplitude reduction of more than 73% discriminated ARN from other infectious uveitis with 75% sensitivity and 90% specificity (area under the curve [AUC] = 0.84), while a reduction greater than 49% discriminated ARN from non-infectious uveitis with 89% sensitivity and 76% specificity (AUC = 0.83). Pre-treatment visual acuity was the strongest predictor of visual prognosis.

CONCLUSIONS: ERG response is significantly reduced in the early stages of ARN. Therefore, ERG may serve as a valuable diagnostic tool for ARN, particularly when specialist examination or definitive diagnosis based on clinical findings is delayed. Given that early treatment improves the prognosis of ARN, this finding highlights the critical role of early diagnosis in preventing vision loss.

Fukuoka, H. Infrared Photography: A Novel Diagnostic Approach for Ocular Surface Abnormalities Due to Vitamin A Deficiency, 2025

Vitamin A deficiency (VAD) remains a significant cause of preventable blindness worldwide, with ocular surface changes representing early manifestations that require prompt recognition and treatment. Conventional examination methods are capable of detecting advanced changes; however, subtle conjunctival abnormalities may be overlooked, potentially delaying the administration of appropriate interventions. We herein present the case of a 5-year-old Japanese boy with severe VAD due to selective eating patterns. This case demonstrates the utility of infrared photography as a novel diagnostic approach for detecting and monitoring conjunctival surface abnormalities. The patient exhibited symptoms including corneal ulcers, night blindness, and reduced visual acuity. Furthermore, blood tests revealed undetectable levels of vitamin A (5 IU/dL), despite relatively normal physical growth parameters. Conventional slit-lamp examination revealed characteristic sandpaper-like conjunctival changes. However, infrared photography (700–900 nm wavelength) revealed distinct abnormal patterns of conjunctival surface folds and keratinization that were not fully appreciated on a routine examination. Following high-dose vitamin A supplementation (4000 IU/day), complete resolution of ocular abnormalities was achieved within 2 months, with infrared imaging objectively documenting treatment response and normalization of conjunctival surface patterns. This case underscores the potential for severe VAD in developed countries, particularly in the context of dietary restrictions, thereby underscoring the significance of a comprehensive dietary history and a meticulous ocular examination. Infrared photography provides a number of advantages, including the capacity for non-invasive assessment, enhanced visualization of subtle changes, objective monitoring of treatment response, and cost-effectiveness due to the use of readily available equipment. This technique represents an underutilized diagnostic modality with particular promise for screening programs and clinical monitoring of VAD-related ocular manifestations, potentially preventing irreversible visual loss through early detection and intervention.

Ueberroth, J. Electroretinographic Response Following Inadvertent Intravitreal Injection of Lidocaine 2%, 2025

PURPOSE: To describe the visual and electroretinographic (ERG) outcomes after inadvertent intravitreal injection of lidocaine.

METHODS: A 75-year-old man with neovascular age-related macular degeneration inadvertently received approximately 0.07 mL of lidocaine 2% intravitreally in his right eye. Serial 30 Hz flicker ERG was performed at 3, 6, and 24 hours postinjection.

RESULTS: Visual acuity decreased to count fingers immediately after the injection and returned to baseline of 20/30 within 24 hours. ERG showed increased amplitudes at 3 hours in the affected eye (47.7 microvolts) relative to the unaffected eye (35.7 microvolts) that normalized at hours 6 (23.5 microvolts OD, 29.1 microvolts OS) and 24 (13.4 microvolts OD, 11.8 microvolts OS). Mean implicit time (26.97 ms OD, 27.0 ms OS) was symmetric.

CONCLUSIONS: In our case, visual acuity reduction and ERG changes specific to 0.07 mL intravitreal lidocaine 2% seem to be transient and may not require any specific therapy other than immediate intraocular pressure control.

Yu, X. Dynamic Changes in Ocular and Retinal Function across Acute Hypobaric Hypoxia, 2025

Visual impairment and intracranial pressure (VIIP) syndrome has been recognized as a major health risk during long-duration spaceflight, but the underlying mechanisms remain incompletely understood. Terrestrial high-altitude hypoxia provides a relevant analog to investigate these processes. In this study, 39 healthy participants were evaluated at baseline (sea level) and during acute exposure to 3,500 m, 4,000 m, and 4,500 m. Measurements included refraction [sphere (SPH), cylinder (CYL)], intraocular pressure (IOP), and electroretinography (ERG). The results demonstrated subtle, non-significant fluctuations in refraction and IOP across different altitudes. ERG responses showed a reduction in amplitude and an increase in latency, especially a significant reduction in the amplitude of the flicker b-wave, suggesting that the inner retinal layer is extremely sensitive to hypoxia. Regression analyses identified a significant negative association between IOP and flicker B-wave amplitude ($\beta = -0.307$, $p = 0.031$), whereas no significant associations were found between refractive status and ERG parameters. These findings suggest that acute hypoxic exposure affects retinal function while subtly altering ocular optics, reflecting aspects of the VIIP syndrome and acute mountain sickness (AMS). Therefore, our findings provide a rationale for future validation of noninvasive ocular measurements, including refraction and ERG, as candidate biomarkers for hypoxia-related visual and neurological risk in both high-altitude and spaceflight environments.

Liu, X. Retinal multimodal-imaging and functional tests in a mitochondrial disease with focal and segmental glomerulosclerosis, 2025

The phenotypes of the adenine-to-guanine transition at position 3243 of mitochondrial DNA (m.3243A>G) are highly variable, with different symptoms observed in different patients. These include mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS); maternally inherited diabetes and deafness syndrome (MIDD); other syndromic conditions; or non-syndromic mitochondrial disorders. Renal involvement associated with this mutation generally manifests as subnephrotic proteinuria, progressive deterioration of kidney function, and increased morbidity. The retinopathies linked to the m.3243A>G mutation have heterogeneous presentations, characterized by variable degrees of retinal pigment epithelium (RPE) atrophy and hyperpigmentation at the posterior pole. As a severe phenotype of the m.3243A>G mutation, MELAS combined with focal and segmental glomerulosclerosis (FSGS) is rare. We herein firstly reported in detail the ophthalmic manifestations of a patient with this condition. Additionally, we reviewed the literature on fundus, ophthalmic electrophysiology, and optical coherence tomography (OCT) findings related to the m.3243A>G mutation.

Igawa, Y. Acquired bipolar cell disorder presenting with photophobia, 2025

BACKGROUND Patients have been recently reported who had a common symptom of unilateral photophobia. The electroretinograms (ERGs) recorded from the eyes of these patients had a negative shape with the a-wave normal to slightly attenuated, and the rod and cone responses severely reduced, i.e., a-wave > b-wave. The patients did not complain of night blindness, and the visual acuity and color vision were relatively well preserved. These patients were diagnosed with acute diffuse occult inner retinopathy (ADOIR). We report our findings in such a case in which the unilateral findings progressed to the fellow eye. In the end, we diagnosed our case with bilateral ADOIR. Case presentation The patient was a 75-year-old woman whose main complaint was photophobia. She had undergone cataract surgery on both eyes by a neighborhood ophthalmologist. However, her symptoms did not improve, and she was referred to the Saitama Medical University Hospital in May 202X. At our initial examination, she did not complain of night blindness, and her decimal visual acuity in the right eye was 1.0 and that of her left eye was 0.9. The fundus photographs and optical coherence tomographic (OCT) images and Goldmann perimetric visual fields were within normal limits. The full-field mixed electroretinograms (ERGs) had a negative shape with severely reduced rod, cone, and flicker responses in the right eye. Multifocal ERGs showed reduced responses only in the macula of both eyes. Conclusions We conclude that our patient had bilateral ADOIR. The ERGs were the key for reaching this diagnosis and would be important for determining the mechanism of photophobia that occurs at the retinal level.

Arnold, N. Cancer-Associated Retinopathy Presenting as Panuveitis Secondary to Minimally Invasive Follicular Thyroid Carcinoma, 2025

PURPOSE: To describe a case of cancer-associated retinopathy (CAR) secondary to follicular thyroid carcinoma. Methods: A single retrospective case was evaluated.

RESULTS: A 68-year-old woman presented with floaters and decreased vision in the right eye and was found to have panuveitis. The left eye subsequently developed panuveitis 6 months later, ultimately resulting in retinal atrophy. Extensive investigations, including vitreous biopsies, imaging, and positron emission tomography, led to a diagnosis of CAR secondary to minimally invasive follicular thyroid carcinoma with serology positive for anti-enolase, antiHSP60, and anti-glyceraldehyde-3-phosphate dehydrogenase.

CONCLUSIONS: Cases of CAR secondary to minimally invasive follicular thyroid carcinoma are rare. Ensuring an early diagnosis and promptly initiating treatment, with a goal of preserving sight, are imperative.

Yu, X. Dynamic neurovascular adaptation of the retina during high-altitude hypoxia: integrated analysis of ERG and OCTA changes in healthy subjects, 2026

Acute hypobaric hypoxia induces rapid neurovascular adjustments in the central nervous system, yet the specific spatiotemporal dynamics of these responses remain incompletely understood. The retina, with its high metabolic demand and direct accessibility, provides a unique noninvasive model to investigate neurovascular coupling dynamics under simulated high-altitude hypoxia. Twenty-one healthy adults underwent ophthalmic evaluations at sea level, during a stepwise ascent to 4,500 m in a hypobaric chamber (simulated altitudes: 3,500 m, 4,000 m, 4,500 m), and during a subsequent recovery phase. Images were acquired 10 min after reaching each plateau. Optical coherence tomography angiography (OCTA) was used to quantify vessel density (VD), perfusion area (PA), and small-vessel density (SVD). Full-field electroretinogram (ERG) was recorded under dark- and light-adapted conditions. Linear mixed-effects models and correlation analyses were used to assess altitude-related changes. The superficial vascular plexus (SVP) exhibited a sustained compensatory vasodilation (increased VD and PA) across all altitudes. In contrast, ERG amplitudes declined significantly at 4,500 m, revealing a functional supply-demand mismatch. Strict statistical analysis revealed a loss of linear neurovascular correlation during hypoxia, while strong correlations re-emerged during the recovery-phase. In addition, physiological parameters did not immediately return to baseline during recovery, indicating a distinct physiological hysteresis. The retina displays differential neurovascular responses during progressive hypoxia. Although the superficial microvasculature mounts a sustained compensatory response, neuronal function decompensates under severe stress. These results suggest that retinal vascular dilation reaches a functional ceiling, leading to neurovascular uncoupling, and that the system exhibits a metabolic lag during recovery.

NEW & NOTEWORTHY This study identifies a critical “functional mismatch” in retinal neurovascular adaptation to acute hypoxia. We demonstrate that while superficial microvasculature sustains compensatory dilation up to simulated 4,500 m, neuronal function significantly declines. This dissociation suggests that vascular autoregulation reaches a functional ceiling, failing to sustain neural activity under severe stress. These findings establish the retina as a sensitive noninvasive model for determining the physiological limits of cerebral oxygen regulation.

Rare Indications / Case Reports

Maranhao B. et al. Investigating the Molecular Basis of Retinal Degeneration in a Familial Cohort of Pakistani Decent by Exome Sequencing, 2015

PURPOSE: To define the molecular basis of retinal degeneration in consanguineous Pakistani pedigrees with early onset retinal degeneration.

METHOD: A cohort of 277 individuals representing 26 pedigrees from the Punjab province of Pakistan was analyzed. Exomes were captured with commercial kits and sequenced on an Illumina HiSeq 2500. Candidate variants were identified using standard tools and analyzed using exomeSuite to detect all potentially pathogenic changes in genes implicated in retinal degeneration.

RESULTS/CONCLUSION: We identified a total of nine causal mutations, including six novel variants in RPE65, LCA5, USH2A, CNGB1, FAM161A, CERKL and GUCY2D as the underlying cause of inherited retinal degenerations in 13 of 26 pedigrees.

We identified causal mutations associated with retinal degeneration in nearly half of the pedigrees investigated in this study through next generation whole exome sequencing. All novel variants detected in this study through exome sequencing have been cataloged providing a reference database of variants common in, and unique to the Pakistani population.

Ullah I. et al. Mutations in phosphodiesterase 6 identified in familial cases of retinitis pigmentosa, 2016

PURPOSE: In the pursuit of determining the genetic basis of autosomal recessive RP, we have collected a large cohort of volunteer participants from highly inbred families, all affected by retinal dystrophies.

METHOD: To delineate the genetic determinants associated with retinitis pigmentosa (RP), a hereditary retinal disorder, we recruited four large families manifesting cardinal symptoms of RP. We localized these families to regions on the human genome harboring the α and β subunits of phosphodiesterase 6 and identified mutations that were absent in control chromosomes.

RESULTS/ CONCLUSION: In conclusion, we report four causal mutations present in consanguineous RP families recruited from the Punjab province of Pakistan. PDE6 is necessary for regulating the concentrations of cyclic guanine monophosphate in the retina and mutations in its subunits have been associated with RP, including a pathogenic connection between PDE6B and congenital stationary night blindness. We have previously reported mutations in both PDE6A and PDE6B that are responsible for RP in our cohort of Pakistani families. We have recruited 4350 families, and of these, we have now localized 11 familial cases to PDE6 genes (PDE6A and PDE6B), suggesting that they contribute approximately 3% of the total genetic load of autosomal recessive RP in our cohort. Determining the genetic cause of RP contributes to our understanding of the disease itself and of the normal physiological function of the retina. A better understanding of the physiology and its underlying pathology will hopefully lead to improved diagnosis and treatment of RP.

Asakawa K. et al. Electroretinography and Pupillography in Unilateral Foveal Hypoplasia, 2016

PURPOSE: The authors describe a 3-year-old boy with unilateral foveal hypoplasia and an absence of other ocular or systemic findings. Electroretinography obtained predominantly affecting cones. Laterality of pupil constriction to red but not to blue light was observed. The colored-light pupil response can be used to predict the retinal state.

METHOD: We have recorded the pupil light response in a patient with unilateral foveal hypoplasia in the absence of other ocular or systemic findings.

RESULTS/ CONCLUSION: One hypothesis for the laterality of pupil constriction to red light is a potential effect on melanopsin-containing retinal ganglion cells in the eye with predominantly affecting cones. Our results provide the functional data supporting this hypothesis. However, the differential diagnosis may include early retinal degeneration and retinopathy of prematurity.8 Consequently, these results indicate that the colored-light pupil response can be used to predict the retinal state in patients with foveal hypoplasia.

Biswas P. et al. A mutation in IFT43 causes non-syndromic recessive retinal degeneration, 2017

PURPOSE: The aim of this work is to identify the molecular cause of autosomal recessive early onset retinal degeneration in a consanguineous pedigree

METHOD: Seventeen members of a four-generation Pakistani family were recruited and underwent a detailed ophthalmic examination. Exomes of four affected and two unaffected individuals were sequenced. Variants were

filtered using exomeSuite to identify rare potentially pathogenic variants in genes expressed in the retina and/or brain and consistent with the pattern of inheritance.

Clinical analysis including electroretinography (ERG), fundus photography, and color vision was performed on four affected members (III: 1, III: 2, III: 7 and III: 8) and two unaffected members of this pedigree (III: 4 and III: 5). Patients' ERG responses were measured at 0 dB while the 30 Hz flicker responses were recorded at 0 dB to a background illumination of 17 to 34 cd/m2 using LKC Technologies, Inc (Gaithersburg, MD).

RESULTS/CONCLUSION: Our studies identified a novel homozygous mutation in the ciliary protein IFT43 as the underlying cause of recessive inherited retinal degeneration. This is the first report demonstrating the involvement of IFT43 in retinal degeneration.

Sheikh S.A. et al. Homozygous Variant in ARL3 Causes Autosomal Recessive Cone Rod Dystrophy, 2019

PURPOSE: Cone rod dystrophy (CRD) is a group of inherited retinopathies characterized by the loss of cone and rod photoreceptor cells, which results in poor vision. This study aims to clinically and genetically characterize the segregating CRD phenotype in two large, consanguineous Pakistani families.

METHOD: Funduscopy, optical coherence tomography (OCT), electroretinography (ERG), color vision, and visual acuity assessments were performed to evaluate the retinal structure and function of the affected individuals. Exome sequencing was performed to identify the genetic cause of CRD. Furthermore, the mutation's effect was evaluated using purified, bacterially expressed ADP-ribosylation factor-like protein 3 (ARL3) and mammalian cells.

RESULTS/ CONCLUSION: Fundus photography and OCT imaging demonstrated features that were consistent with CRD, including bull's eye macular lesions, macular atrophy, and central photoreceptor thinning. ERG analysis demonstrated moderate to severe reduction primarily of photopic responses in all affected individuals, and scotopic responses show reduction in two affected individuals. The exome sequencing revealed a novel homozygous variant (c.296G>T) in ARL3, which is predicted to substitute an evolutionarily conserved arginine with isoleucine within the encoded protein GTP-binding domain (R99I). The functional studies on the bacterial and heterologous mammalian cells revealed that the arginine at position 99 is essential for the stability of ARL3.

Our study uncovers an additional CRD gene and assigns the CRD phenotype to a variant of ARL3. The results imply that cargo transportation in photoreceptors as mediated by the ARL3 pathway is essential for cone and rod cell survival and vision in humans.

Endres D. et al. Heteroplasmic Point Mutation in the MT-ND4 Gene (m.12015T>C; p.Leu419Pro) and Comorbid Polyglandular Autoimmune Syndrome Type 2, 2019

PURPOSE: To our knowledge, this is the first case report of a patient with MELAS syndrome with comorbid autoimmune polyglandular syndrome type 2. This aspect is clinically important, as shown in the patient's history. Addison's disease and MELAS syndrome (lactate acidosis/myopathy) share clinical features with respect to weakness, fatigue, and abdominal complaints such as nausea or diarrhea. Hence, it is important to think of both diseases when considering the differential diagnosis. Additionally, our patient was tested positive for further antibodies. It is important to recognize these immunological changes to prevent end organ damage.

METHOD: We present the case of a 25-year-old female patient with dysexecutive syndrome, muscular fatigue, and continuous headache. Half a year ago, she fought an infection-triggered Addison crisis. As the disease progressed, she had two epileptic seizures and stroke-like episodes with hemiparesis on the right side. [Following diagnostic steps were done] Psychiatric examination, Psychiatric examination, Family history, Genetic testing, Basic blood/urine analyses, Immunological blood testing, Cerebrospinal fluid analyses, Cerebral magnetic resonance imaging, magnetic resonance spectroscopy, Electroencephalography, Electromyography, Lactate ischemia test, Magnetic resonance imaging of thigh and lower leg, Muscle biopsy, Ophthalmological examinations: For visual electrodiagnostic testing light adapted electroretinogram was recorded from both eyes using RETeval device from LKC-Technologies. Both eyes showed normal cone function in response to the photopic-flash protocol and normal ganglion cell function with the stimulation protocol for the photopic negative response. Normative data were provided by LKC-Technologies. Heart examinations, Otorhinolaryngologic examination, Ultrasound of the carotids, Thyroid sonography, Gastroscopy, Neuropsychological tests

RESULTS/ CONCLUSION: In summary, to our knowledge this is the first case presentation of a patient with atypical MELAS syndrome presenting with a neuropsychiatric syndrome of predominantly executive dysfunction, together with a polyglandular autoimmune syndrome type 2, and a heteroplasmic point mutation in the MT-ND4 gene. The recognition of such constellations is important for further research and clinical differential diagnosis in complex neuropsychiatric cases.

Screening for autoimmune alterations in those patients is important to prevent damage to end organs.

Lindegger, D. et al. Transient Electroretinographic Changes during Light-Induced Amaurosis in Severe Carotid Artery Stenosis Measured with a Novel Portable Handheld Device, 2019

Case presentation. No abstract available.

BACKGROUND: Light-induced amaurosis (LIA) is a very rare manifestation of ocular ischemic syndrome that is thought to be associated with impairment in the regeneration of the retinal photopigment due to structural changes of the retina as a result of chronic ischemia.

Etheridge T. et al. Ocular evaluation and genetic test for an early Alström Syndrome diagnosis, 2020

PURPOSE: We present 3 cases of Alström syndrome (ALMS) that highlight the importance of the ophthalmic exam, as well as the diagnostic challenges and management considerations of this ultra-rare disease.

OBSERVATIONS: The first case is of a 2-year-old boy with history of spasmus nutans who presented with head bobbing and nystagmus. The second patient is a 5-year-old boy with history of infantile dilated cardiomyopathy status post heart transplant, Burkitt lymphoma status post chemotherapy, obesity, global developmental delay, and high hyperopia previously thought to have cortical visual impairment secondary to heart surgery/possible ischemic event. This patient presented with nystagmus, photophobia, and reduced vision. The third case involves a 8-year-old boy with history of obesity, bilateral optic nerve atrophy, hyperopic astigmatism, exotropia, and nystagmus. Upon presentation to the consulting pediatric ophthalmologist, none of the patients had yet been diagnosed with ALMS. All 3 cases were subsequently found to have an electroretinogram (ERG) that exhibited severe global depression and to carry ALMS1 pathogenic variants.

CONCLUSION AND IMPORTANCE: ALMS is an autosomal recessive disease caused by ALMS1 variations, characterized by cone-rod dystrophy, obesity, progressive sensorineural hearing loss, cardiomyopathy, insulin resistance, and multiorgan dysfunction. Retinal dystrophy diagnosis is critical given clinical criteria and detection rates of genetic testing. Early diagnosis is extremely important because progression to flat ERG leads to the inability to differentiate between rod-cone or cone-rod involvement, either of which have their own differential diagnoses. In our series, the ophthalmic exam and abnormal ERG prompted further genetic testing and the subsequent diagnosis of ALMS. Multidisciplinary care ensures the best possible outcome with the ophthalmologist playing a key role.

Hagag AM. et al. Prospective deep phenotyping of choroideremia patients using multimodal structure-function approaches, 2020

OBJECTIVE: To investigate the retinal changes in choroideremia (CHM) patients to determine correlations between age, structure and function.

SUBJECTS/METHODS: Twenty-six eyes from 13 male CHM patients were included in this prospective longitudinal study. Participants were divided into <50-year (n = 8) and ≥50-year (n = 5) old groups. Patients were seen at baseline, 6-month, and 1-year visits. Optical coherence tomography (OCT), OCT angiography, and fundus autofluorescence were performed to measure central foveal (CFT) and subfoveal choroidal thickness (SCT), as well as areas of preserved choriocapillaris (CC), ellipsoid zone (EZ), and autofluorescence (PAF). Patients also underwent functional investigations including visual acuity (VA), contrast sensitivity (CS), colour testing, microperimetry, dark adaptometry, and handheld electroretinogram (ERG). Vision-related quality-of-life was assessed by using the NEI-VFQ-25 questionnaire.

RESULTS: Over the 1-year follow-up period, progressive loss was detected in SCT, EZ, CC, PAF, and CFT. Those ≥50-years exhibited more structural and functional defects with SCT, EZ, CC, and PAF showing strong correlation with patient age (rho ≤ -0.47, p ≤ 0.02). CS and VA did not change over the year, but CS was significantly correlated with age (rho = -0.63, p = 0.001). Delayed to unmeasurable dark adaptation, decreased colour discrimination and no detectable ERG activity were observed in all patients. Minimal functional deterioration was observed over one year with a general trend of slower progression in the ≥50-years group.

CONCLUSIONS: Quantitative structural parameters including SCT, CC, EZ, and PAF are most useful for disease monitoring in CHM. Extended follow-up studies are required to determine longitudinal functional changes.

Katagiri S et al. RDH5 -Related Fundus Albipunctatus in a Large Japanese Cohort, 2020

PURPOSE: To investigate clinical characteristics of RDH5-related fundus albipunctatus (FAP) in a Japanese cohort.

METHOD: Twenty-five patients from 22 pedigrees with RDH5-related FAP were studied. Ophthalmic medical records were reviewed. For genetic analysis, either Sanger sequencing of the RDH5 gene or whole-exome sequencing was performed.

RESULTS/ CONCLUSION: In optical coherence tomography, macular involvement was observed in 12 patients (24 eyes). Ten patients (83.3%) who had good BCVA (0.10 or better) exhibited diffuse disruption of the outer retina with foveal sparing, and two patients (16.7%) exhibited diffuse disruption throughout the macula and decreased BCVA.[...] Full-field electroretinography showed extinguished or severely decreased rod responses in all 23 examined patients, whereas decreased cone responses were seen in 17 patients (73.9%).

Kato, K. Case of Cystoid Macular Edema Induced by Systemic Administration of Paclitaxel: Evaluations with Electroretinograms, 2021

PURPOSE: To report abnormal full-field electroretinograms (ERGs) in a patient with cystoid macular edema (CME) induced by systemic paclitaxel.

METHODS: This is an observational case report. Full-field ERGs were recorded to evaluate the retinal function using the RETeval system and conventional ERGs using contact lens electrodes with built-in white light-emitting diodes. Optical coherence tomography (OCT) was also used to assess the retinal morphology.

RESULTS: A 70-year-old man, who was diagnosed with gastric cancer, had undergone gastrectomy. Subsequently, systemic paclitaxel was administered once a week as an adjuvant therapy. After the tenth course of paclitaxel, he experienced blurred vision in both eyes and visited our department of ophthalmology. OCT revealed the presence of CME in both eyes, and the RETeval flicker ERGs showed a marked reduction in the amplitudes and a prolongation of the implicit times in both eyes. Conventional ERGs showed that the amplitudes of the oscillatory potentials (OPs) were also severely attenuated. The abnormal OCT findings and reduced visual acuity recovered to normal at 1 and 2 months, respectively, after the discontinuation of paclitaxel. However, the flicker ERGs did not recover to normal values until 4 months after the discontinuation of paclitaxel.

CONCLUSION: These results suggest that the ERGs can be used to monitor the changes in the overall retinal function in patients receiving paclitaxel.

Matsushima, T. Electrophysiological Monitoring of Focal and Entire Retinal Function during Treatment with Intravitreal Methotrexate for Intraocular Lymphoma, 2021

We describe the electroretinographic findings of a case of primary intraocular lymphoma (PIOL) wherein the patient received intravitreal injections of methotrexate (ivMTX). A 62-year-old man developed blurred vision and complained of decreased visual acuity (VA) in his right eye. Fundus examination showed vitreous opacity and multiple subretinal yellowish lesions. Optical coherence tomography (OCT) revealed subretinal and intraretinal infiltrations. The full-field electroretinogram (ffERG) showed subnormal combined rod-cone response and multifocal electroretinogram (mfERG) recorded using skin electrodes showed severe attenuation of the response compared with the other eye. Pars prana vitrectomy, phacoemulsification, and lens implantation were performed to remove the opacity, and vitreous biopsy revealed a high ratio of interleukin 10–6 (76.0). There was no systemic malignant lesion, and the patient was diagnosed with PIOL. Treatment with ivMTX (400 μg/0.1 mL) was started. One month later, the intraretinal infiltration had disappeared, and mfERG revealed recovery of the response density from the central area. Two months later, OCT showed recovery of the foveal ellipsoid and interdigitation zones, and VA recovered to 20/17; mfERG showed maintenance of macular function. However, the amplitude of a- and b-waves in the ffERG gradually decreased. Macular function recovered, but there was also a decrease in total retinal function. mfERG and ffERG recorded using skin electrodes were useful in monitoring macular and entire retinal function with repeated examinations and showed recovery and maintenance of macular function in a case of PIOL treated with ivMTX.

Sather, R. Septo-optic dysplasia presenting with nystagmus, pseudo-disc edema, and fovea hypoplasia, 2022

BACKGROUND: Septo-optic dysplasia (SOD) is a condition that affects the early development of the brain and eyes. It presents with a combination of optic nerve hypoplasia, brain midline structure abnormalities, and pituitary gland hypoplasia.

METHODS: This is a case report of a 4-year-old male who presented with low amplitude horizontal nystagmus and decreased visual acuity 20/60 OU. Further imaging and electrophysiology were conducted to classify the ocular presentation

RESULTS: No iris transillumination was noted, but foveal hypoplasia and disc edema were evident on fundus examination. This prompted neurology consultation and MRI imaging. The MRI was consistent with the diagnosis of SOD showing hypoplasia of the optic nerves, chiasm, and tracts and an absent septum pellucidum, but with normal pituitary development and function. Lumbar puncture and intracranial pressure were normal. Genetic testing identified one pathogenic variant in the SLC45A2, indicating carrier status for oculocutaneous albinism type 4 (OCA4). Flash Visual Evoked Potentials (VEPs) were consistent with chiasm dysfunction or hypoplasia rather than the chiasmal misrouting of OCA.

CONCLUSION: This case report further elaborates the phenotypic variation of SOD, with the finding of blurred disc margins, in the absence of the typical optic nerve double ring sign and with normal intracranial pressure. The findings of fovea hypoplasia and blond fundi lead to the suspicion of OCA either as a separate diagnosis with a second pathogenic variant in SCL45A2 not yet identified or in association with SOD. This case highlights the importance of electrophysiology to help distinguish chiasmal hypoplasia or dysfunction from OCA misrouting.

Vanden Heuvel, C. MFRP variant results in nanophthalmos, retinitis pigmentosa, variability in foveal avascular zone, 2022

BACKGROUND: Membrane frizzled-related protein (MFRP) plays a critical role in ocular development. MFRP mutations are known to cause nanophthalmos and, in some cases, retinitis pigmentosa, foveoschisis, and/or optic nerve head (ONH) drusen. The broad clinical spectrum of MFRP mutations necessitates further investigation of specific genotype-phenotype relationships.

MATERIALS AND METHODS: We reviewed ophthalmologic and genetic medical records of two affected siblings and one unaffected sibling.

RESULTS: Genetic testing revealed variants MFRP c.855T>A, p.(Cys285*) and MFRP c.1235T>C, p.(Leu412Pro) in trans in the two affected siblings. In both cases, photopic and scotopic responses were markedly reduced on electroretinogram (ERG), with greater decrease in scotopic function. Optical coherence tomography for both siblings revealed non-cystoid thickening. Blunted foveal reflexes were also observed in both siblings. Notably, foveal avascular zone abnormalities were seen on fundus autofluorescence in only one affected sibling.

CONCLUSIONS: MFRP-related ocular disease may be underrecognized due to its presentation with high hyperopia and possibly subtle retinal findings. Presence of variants MFRP c.855T>A, p.(Cys285*) and MFRP c.1235T>C, p.(Leu412Pro) in trans resulted in nanophthalmos and retinitis pigmentosa without associated foveoschisis or ONH drusen in our patients, consistent with the incomplete phenotype previously described in Neri et al. Abnormalities in the foveal avascular zone have been noted in other case studies and were inconsistently associated with the variants described here, representing a potential area for future investigation.

Yousaf, S. Delineating the Molecular and Phenotypic Spectrum of the CNGA3-Related Cone Photoreceptor Disorder in Pakistani Families, 2022

Cone photoreceptor dysfunction represents a clinically heterogenous group of disorders characterized by nystagmus, photophobia, reduced central or color vision, and macular dystrophy. Here, we described the molecular findings and clinical manifestations of achromatopsia, a partial or total absence of color vision, co-segregating with three known missense variants of CNGA3 in three large consanguineous Pakistani families. Fundus examination and optical coherence tomography (OCT) imaging revealed myopia, thin retina, retinal pigment epithelial cells loss at fovea/perifovea, and macular atrophy. Combination of Sanger and whole exome sequencing revealed three known homozygous missense variants (c.827A>G, p.(Asn276Ser); c.847C>T, p.(Arg283Trp); c.1279C>T, p.(Arg427Cys)) in CNGA3, the α-subunit of the cyclic nucleotide-gated cation channel in cone photoreceptor cells. All three variants are predicted to replace evolutionary conserved amino acids, and to be pathogenic by specific in silico programs, consistent with the observed altered membrane targeting of CNGA3 in heterologous cells. Insights from our study will facilitate counseling regarding the molecular and phenotypic landscape of CNGA3-related cone dystrophies.

Wygledowska-Promienska, D. Aland Island Eye Disease with Retinoschisis in the Clinical Spectrum of CACNA1F-Associated Retinopathy—A Case Report, 2024

Aland island eye disease (AIED), an incomplete form of X-linked congenital stationary night blindness (CSNB2A), and X-linked cone-rod dystrophy type 3 (CORDX3) display many overlapping clinical findings. They result from mutations in the CACNA1F gene encoding the α1F subunit of the Cav1.4 channel, which plays a key role in neurotransmission from rod and cone photoreceptors to bipolar cells. Case report: A 57-year-old Caucasian man who had suffered since his early childhood from nystagmus, nyctalopia, low visual acuity and high myopia in both eyes (OU) presented to expand the diagnostic process, because similar symptoms had occurred in his 2-month-old grandson. Additionally,

the patient was diagnosed with protanomalous color vision deficiency, diffuse thinning, and moderate hypopigmentation of the retina. Optical coherence tomography of the macula revealed retinoschisis in the right eye and foveal hypoplasia in the left eye. Dark-adapted (DA) 3.0 flash full-field electroretinography (ffERG) amplitudes of a-waves were attenuated, and the amplitudes of b-waves were abolished, which resulted in a negative pattern of the ERG. Moreover, the light-adapted 3.0 and 3.0 flicker ffERG as well as the DA 0.01 ffERG were consistent with severely reduced responses OU. Genetic testing revealed a hemizygous form of a stop-gained mutation (c.4051C>T) in exon 35 of the CACNA1F gene. This pathogenic variant has so far been described in combination with a phenotype corresponding to CSNB2A and CORDX3. This report contributes to expanding the knowledge of the clinical spectrum of CACNA1F-related disease. Wide variability and the overlapping clinical manifestations observed within AIED and its allelic disorders may not be explained solely by the consequences of different mutations on proteins. The lack of distinct genotype–phenotype correlations indicates the presence of additional, not yet identified, disease-modifying factors.

Szeligowski, T. Multimodal Evaluation and Management of Wagner Syndrome—Three Patients from an Affected Family, 2024

Wagner syndrome is a rare autosomal dominant vitreoretinopathy caused by mutations in chondroitin sulphate proteoglycan 2 (CSPG2)/Versican (VCAN). Here, we present a retrospective case series of a family pedigree with genetically confirmed Wagner syndrome (heterozygous VCAN exon 8 deletion), as follows: a 34-year-old mother (P1), 12-year-old daughter (P2), and a 2-year-old son (P3). The phenotype included early-onset cataract (P1), optically empty vitreous with avascular membranes (P1, 2), nasal dragging of optic nerve heads associated with foveal hypoplasia (P1, 2), tractional retinoschisis on optical coherence tomography (P2), and peripheral circumferential vitreo-retinal interface abnormality resembling white-without-pressure (P3) progressing to pigmented chorioretinal atrophy (P1, 2). P2 developed a macula-off retinal detachment, which was treated initially with encircling band + vitrectomy + gas, followed by vitrectomy + heavy silicone oil tamponade for re-detachment from new inferior breaks. Strong vitreo-retinal adhesion was noted intraoperatively, which prevented the separation of posterior hyaloid beyond the equator. Electroretinograms from P1&2 demonstrated attenuated b-waves, a-waves, and flicker responses in light- and dark-adapted conditions, suggestive of generalised retinal dysfunction. Our patients demonstrated the clinical spectrum of Wagner syndrome, highlighting nasal dragging with foveal disruption as a distinguishing feature from other inherited vitreoretinopathies. Surgical outcomes demonstrate significant challenges in managing vitreo-retinal traction and need for further research into strategies to prevent sight loss.

Ceradini, D. Combined Whole Eye and Face Transplant Microsurgical Strategy and 1-Year Clinical Course, 2024

IMPORTANCE: Catastrophic facial injury with globe loss remains a formidable clinical problem with no previous reports of reconstruction by whole eye or combined whole eye and facial transplant.

OBJECTIVE: To develop a microsurgical strategy for combined whole eye and facial transplant and describe the clinical findings during the first year following transplant.

DESIGN, SETTING, AND PARTICIPANT: A 46-year-old man who sustained a high-voltage electrical injury with catastrophic tissue loss to his face and left globe underwent combined whole eye and face transplant using personalized surgical devices and a novel microsurgical strategy at a specialized center for vascularized composite allotransplantation.

MAIN OUTCOMES AND MEASURES: Reperfusion and viability of the whole eye and facial allografts, retinal function, and incidence of acute rejection.

RESULTS: The patient underwent a combined whole eye and face transplant from an immunologically compatible donor with primary optic nerve coaptation and conventional postoperative immunosuppression. Globe and retinal perfusion were maintained throughout the immediate postoperative period, evidenced by fluorescein angiography. Optical coherence tomography demonstrated atrophy of inner retinal layers and attenuation and disruption of the ellipsoid zone. Serial electroretinography confirmed retinal responses to light in the transplanted eye. Using structural and functional magnetic resonance imaging, the integrity of the transplanted visual pathways and potential occipital cortical response to light stimulation of the transplanted eye was demonstrated. At 1 year post transplant (postoperative day 366), there was no perception of light in the transplanted eye.

CONCLUSIONS AND RELEVANCE: This is the first report of whole eye transplant combined with facial transplant, demonstrating allograft survival including rejection-free graft survival and electroretinographic measurements indicating retinal response to light stimuli. These data highlight the potential for clinical allotransplantation for globe loss.

Sather, R. Case report on a de novo variant in the X-linked PRPS1 gene presenting with retinal dystrophy, severe tremors, and ataxia in a female patient, 2024

Case Summary: The patient is a 42-year-old female who presented with a de novo missense variant in the PRPS1 gene. Her phenotype includes asymmetric retinal dystrophy with sensory esotropia, congenital sensorineural hearing loss, neuropathy, and severe tremors with recent-onset ataxia. This contributes a new presentation of ophthalmic and neurological findings to the literature.

Cheng, Y. Bilateral choroidal ganglioneuroma: a comprehensive analysis of vision decline in a 6-year-old boy, 2024

Case Summary: We write to present a 6-year-old boy with bilateral choroidal ganglioneuroma (CG) by comprehensive multimodal imaging (MMI) in a duration of 6-year follow-up. To our knowledge, this is the first case report with elaborate data to delineate the natural history of visual function and MMI in a boy with rare bilateral CG, confirmed by choroid biopsy. Due to the rarity of CG, to date, extremely limited data are documented. Our team summarized the common features based on published reports.

Krzeminska, Y. HLA-A29 Negative Birdshot-like Chorioretinopathy Associated with Vitiligo—Case Report, 2024

A 54-year-old, one-eyed Caucasian male was admitted to the Ophthalmology Clinic due to a gradual deterioration of vision in the right eye for approximately two weeks. The patient denied any trauma or viral infection during this time. On the day of admission, the patient's best corrected visual acuity (BCVA) in the right eye was 0.5 on the Snellen scale. The patient's left eye had been atrophied for several years, with no light perception and no visibility of the fundus due to previous trauma and multiple surgeries. Ophthalmologic examination of the anterior segment and vitreous body of both eyes showed no signs of inflammation. Fundus examination of the right eye revealed scattered inflammatory foci, creamy-yellow and round, visible in all sectors. Laboratory tests, imaging studies, optical coherence tomography (OCT) angiographies, OCTs of the macula and optic nerve head, fluorescein angiographies (FAs), electroretinograms (ERGs), and visual field tests were performed. These examinations led to a diagnosis of a disease resembling birdshot-like chorioretinopathy. Immunogenetic testing of the patient did not reveal the presence of human leukocyte antigen (HLA)-A29. Dermatological and immunological consultations were conducted, and a differential diagnosis was made. Due to the reduced visual acuity (VA) observed and the inability to assess the left eye, a high-dose corticosteroid therapy was initiated, which was gradually tapered, along with the application of an immunosuppressive drug. The course of the disease was typical for birdshot chorioretinopathy, with chronic periods of remissions and exacerbations. The patient's clinical improvement was only achieved after co-administration of general corticosteroids at a dose of 0.5–1 mg/kg/day, mycofenolate mofetil, and periocular (sub-Tenon's) triamcinolone.

Karthik, N. Vitamin A deficiency masquerading as cancer-associated retinopathy, 2025

PURPOSE: To report a case of severe vitamin A deficiency (VAD) initially misdiagnosed as cancer-associated retinopathy (CAR), highlighting diagnostic pitfalls and the importance of nutritional assessment in patients with complex medical histories.

OBSERVATIONS: A 70-year-old woman with metastatic colon cancer and prior gastric bypass presented with progressive bilateral vision loss, nyctalopia, and positive antiretinal autoantibodies suggestive of CAR. Detailed evaluation revealed profound VAD (<0.03 mg/L), likely related to malabsorption. The patient was treated with intramuscular and oral vitamin A, resulting in rapid improvement of visual acuity, retinal structure (OCT and FAF), and electroretinography findings.

CONCLUSIONS AND IMPORTANCE: This case underscores that VAD can clinically mimic CAR and that reliance on antiretinal autoantibody testing alone carries a high risk of false positives. A focused clinical evaluation — including nutritional status — is critical before initiating immunosuppressive therapy in patients with vision loss and systemic disease.

Wójcik-Niklewska, B. Early-Onset Retinal Dysfunction Associated with Novel WDR19 Variants in Sensenbrenner Syndrome, 2025

Sensenbrenner syndrome, or cranioectodermal dysplasia (CED), is a rare autosomal recessive ciliopathy characterized by craniofacial, skeletal, ectodermal, and renal abnormalities. Ocular involvement, though infrequent, can include retinal dystrophy with early-onset visual impairment. We report a case of a 2-year-old boy with classic clinical features of CED and significant ocular findings. Genetic testing revealed two novel compound heterozygous variants in the WDR19 gene—c.1778G>T and c.3536T>G—expanding the known mutational spectrum associated with this condition. Ophthalmologic evaluation demonstrated bilateral optic nerve hypoplasia, high hyperopia, and severely reduced ERG responses, consistent with global retinal dysfunction. Fundoscopy revealed optic disk pallor, vessel attenuation, and peripheral pigment changes. Multisystem findings included postaxial polydactyly, brachydactyly, short stature, hypotonia, and stage 2 chronic kidney disease. This case highlights the importance of early ophthalmologic screening in suspected CED and underscores the utility of ERG in detecting early retinal involvement. The identification of two previously undescribed WDR19 variants contributes to genotype–phenotype correlation in CED and emphasizes the need for ongoing documentation to guide diagnosis, management, and genetic counseling.

Fang, X. De novo variant in GUCY2D gene causing atypical cone-rod dystrophy in a consanguineous family and literature review, 2025

AIM: To analyze the pathogenicity and clinical features of patients in a consanguineous cone-rod dystrophy (CRD) family due to heterozygous variants in the GUCY2D gene.

METHODS: Whole exome sequencing was used to screen for pathogenic genes and candidate pathogenic variants were obtained by bioinformatics analysis. Sanger sequencing was used for validation and familial co-segregation analysis to determine pathogenic variants. Pymol software was applied to produce a 3D structure image of the protein to analyze the structural and functional alterations of the protein. The pathogenicity of genetic variants was evaluated according to ACMG guidelines.

RESULTS: The chief clinical symptoms of this proband included obvious visual impairment, protanopia and deuteranopia, peripheral punctate pigment, arteriolar attenuation, structural and functional abnormalities revealed by optical coherence tomography (OCT) and electroretinography (ERG) including thinning of the outer retinal layer, a discontinuous external limiting membrane (ELM) and ellipsoid zone (EZ), granular hyperreflective projections between the retinal pigment epithelium and the interdigitation zone, severe attenuation of photopic responses with mild reduced scotopic responses. Whole-exome sequencing revealed that the proband carried a heterozygous variant of the GUCY2D gene: c.2512C>T: p.Arg838Cys. Three-dimensional molecular structure analysis of the protein revealed that amino acid 838 was mutated from polar positively charged arginine to polar uncharged cysteine, and the spatial structure of the protein changed greatly. Sanger sequencing co-segregation analysis confirmed that such a variant was detected in neither the phenotypically normal parents nor the daughter of the proband, which was presumed to be a de novo one. The variant was determined to be pathogenic according to ACMG guidelines. The heterozygous variant at the same site was detected in the abnormal proband's son with moderate attenuation of photopic electroretinographic responses and normal scotopic electroretinographic responses, supporting autosomal dominant inheritance.

CONCLUSION: The de novo variant causing atypical autosomal dominant CRD is identified in a Chinese consanguineous family and this variant passes through this family in an autosomal dominant mode of inheritance, revealing the complex diversity and unpredictability of the inheritance mode for common single-gene genetic disease.

Nishina, S. Novel biallelic CDK9 variants are associated with retinal dystrophy without CHARGE-like malformation syndrome, 2025

Cyclin-dependent kinase 9 (CDK9) phosphorylates the C-terminal domain of RNA polymerase II (RNAPII) to regulate transcription. Previously, we reported that an 8-year-old boy with the biallelic CDK9 variants p.A288T and p.R303C exhibited a CHARGE-like malformation syndrome in which retinal dystrophy was a distinguishing feature. This dystrophy was caused by the decreased CDK9 kinase activity associated with these variant alleles [wild-type (WT) > A288T > R303C]. In this study, we describe a female patient who also bears biallelic CDK9 variants but displays retinal dystrophy without a CHARGE-like malformation syndrome. Trio-based whole-exome sequencing identified a new variant CDK9 allele, p.P321S, that occurred de novo in the patient. As a result, this female patient displayed compound heterozygous variants composed of the p.A288T CDK9 variant of maternal origin plus the novel p.P321S variant. With respect to reduced kinase activity, the new variant could be ranked as WT > P321S > A288T. Thus, our study raises a possibility that retinal dystrophy can arise with or without a CHARGE-like malformation syndrome depending on the level of kinase activity associated with the combination of variant CDK9 alleles present.