Abstracts

“The abstracts have been edited to a standard format by the Scientific Committee. We have made every effort to respect the intended meaning in the original submissions and apologise for any inadvertent misinterpretation.”

Wednesday 20th June 2018, 8:30–10:00

Session 1: Paper Session — Genetics of photoreceptors

1.01 Correlating structure function relationships in Usher syndrome: Identifying best correlates for natural history studies in preparation for therapies

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Purpose: To investigate the visual functional measures including visual acuity (VA), full field electroretinogram (ffERG) and pattern electroretinogram (PERG) in Usher syndrome patients and correlate them with ultra-widefield autofluorescence (UW-FAF) and optical coherence tomography (OCT) findings in Usher syndrome (USH).

Methods: Clinical records for patients with Usher syndrome who attended the Save Sight Institute, a tertiary referral centre for electrophysiology and inherited eye disorders, between 2012 and 2017 were reviewed. Clinical data including age, gender, VA, and molecular genetic results were recorded. Results from ffERG and PERG were collected. UW-FAF images were qualitatively graded to identify hypo/hyper fluorescence patterns in the peripheral fundus. Macular OCT scans were assessed to identify the presence of cystoid macular edema (CME) and the linear extent of retina with preserved outer retinal layers (macular island). Macular thickness (MT) was calculated as the average thickness of the ETDRS map as generated by macular OCT volumes. UW-FAF patterns and OCT features were correlated with functional measurements.

Results: Thirty-six eyes from 18 subjects (10 males, mean age 31 years, range 9-65) were included. Genetic results were available for six patients with USH2A and MY07A being identified in three patients each. Four patterns of changes were identified on UW-FAF (granular 55%, annular 11%, bone spicule 17%, and patchy 17%). Patient with patchy peripheral fundus appearance demonstrated worse VA, in comparison to those with granular ($p<.0001$) and bone spicule ($P=0.0179$) patterns, but less than those with annular. Granular pattern was more prevalent in younger subjects (<30 years). CME was present in 41.7% of eyes. Mean MT was 271 ± 35 µm. Mean foveal island extent was 2405 ± 1528 µm. Mean VA was 0.22 ± 0.3 logMAR ($p<0.04$ and $p<0.0001$, respectively). Macular island extent correlated with VA ($r=-0.69$, $p<0.0001$), PERG P50 ($r=0.49$, $p=0.004$) and PERG N95 ($r=-0.47$, $p=0.007$). MT showed a strong correlation with VA ($r=-0.78$, $p<0.0001$). VA was not different in patients with and without CME.

Conclusions: Structural changes identified on OCT and UW-FAF strongly correlated with visual function measures including VA and PERG parameters. This study identified a set of structural and functional parameters [OCT defined central foveal island and macular thickness, visual acuity, PERG P50, and UW-FAF pattern (patchy)] that could provide strong measures for natural history analysis and represent outcome biomarkers in therapeutic clinical trials for patients diagnosed with Usher syndrome.

1.02 A rod-cone dysfunction syndrome due to biallelic mutations in GUCY2D

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Purpose: This report aims to characterize a novel form of autosomal recessive rod-cone dysfunction syndrome with some similarities to rare forms of CSNB.

Methods: Three patients were ascertained with a history of lifelong night blindness, no fundus features typical of retinitis pigmentosa, and an

unusual functional phenotype on ISCEV-standard ERG testing. Detailed clinical examination included visual acuity and colour vision, fundus photography and fundus autofluorescence (FAF) imaging and spectral domain optical coherence tomography (OCT). The patients were genotyped by whole exome or whole genome sequencing.

Results: The DA 0.01 ERG was undetectable in all cases. The DA 10.0 ERG a-waves were subnormal and b-waves had short peak time in all cases; waveforms were electronegative in two of three cases. The LA 30Hz ERGs were significantly delayed with normal amplitude; LA 3.0 b-waves were delayed in all and subnormal in two of three. Two of three cases show mild worsening of LA ERG timing over periods of 7 and 13 years; one other was stable over 2 years. Clinical examination showed normal or near-normal visual acuity and normal colour vision in all patients. FAF showed bilateral hyperautofluorescent spots in the fovea, which corresponded to discrete disruption of the ellipsoid zone on OCT. Molecular analysis showed biallelic mutations in GUCY2D.

Conclusions: This report documents a distinctive autosomal recessive rod-cone dysfunction syndrome associated with biallelic mutations in GUCY2D, encoding RetGC. The lack of photoreceptor degeneration, clinical features and relatively high degree of ERG stability are distinct but with some similarities to rare forms of CSNB. Biallelic mutations in GUCY2D are usually associated with Leber congenital amaurosis. This study illustrates the phenotypic variability of GUCY2D retinopathies and highlights the importance of RetGC in rod photoreceptor function.

1.03 Long-term safety of human retinal progenitor cell transplantation in retinitis pigmentosa patients

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Purpose: Retinitis pigmentosa is a common genetic disease that causes retinal degeneration and blindness, for which there is currently no curable treatment available. Vision preservation was observed in retinitis pigmentosa animal models after retinal stem cell transplantation. However, long-term safety studies and visual assessment have not been thoroughly tested in retinitis pigmentosa patients.

Methods: In our pre-clinical study, purified human fetal-derived retinal progenitor cells (RPCs) were transplanted into the diseased retina of Royal College of Surgeons (RCS) rats, a model of retinal degeneration. Based on these results, we conducted a Phase 1 clinical trial to establish the safety and tolerability of transplantation of RPCs in eight patients with advanced retinitis pigmentosa. Patients were studied for 24 months.

Results: After RPC transplantation in RCS rats, we observed moderate recovery of vision and maintenance of the outer nuclear layer thickness. Most importantly, we did not find tumor formation or immune rejection. In the retinitis pigmentosa patients given RPC injections, we also did not observe immunological rejection or tumorigenesis when immunosuppressive agents were not administered. We observed a significant improvement in visual acuity ($P < 0.05$) in five patients and an increase in retinal sensitivity of pupillary responses in three of the eight patients between 2 and 6 months after the transplant, but this improvement did not appear by 12 months.

Conclusions: Our study for the first time confirmed the long-term safety and feasibility of vision repair by stem cell therapy in patients blinded by retinitis pigmentosa.

1.04 Phenotypical variations of cone dystrophy with normal fundus appearance caused by POC1B gene mutations

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Purpose: Mutations in POC1B gene are known to result in a defect of the photoreceptor sensory cilium and lead to autosomal-recessive cone-rod dystrophy or syndromic Leber's congenital amaurosis (Roosing S et al. *Am J Hum Genet* 2014;95:131-42; Beck B et al. *Hum Mutat* 2014;35:1153-62). We have recently reported that mutations in POC1B gene cause autosomal recessive cone dystrophy with normal fundus appearance (Kominami A et al. *Ophthalmic Genet* 2018;39:255-62). We have investigated phenotypical characteristics of eight patients from seven families harbouring POC1B gene mutations in a cohort of Japan eye genetics consortium (JEGC).

Methods: Whole-exome sequence with targeted analysis identified homozygous or compound heterozygous mutations of the POC1B gene in eight out of 1035 cases (seven out of 548 families) in the JEGC database. Comprehensive ophthalmological examinations were performed for these patients which included best corrected visual acuity (VA), visual field testing, fundus photography/funduscopy, fundus autofluorescence (AF) imaging, optical coherence tomography (OCT), full-field ERGs, and multifocal ERGs.

Results: There were four males and four females, whose median age of onset/examination was 21.0/39.0 years (range, 8-23/22-67). Chief complaint was either photophobia (seven cases) or reduced visual acuity (four cases). The logMAR VA in the right/left eye ranged from -0.08 to 1.8/-0.08 to 1.8. Visual field testing revealed central scotoma in four cases and para-central scotoma in three cases. Funduscopic appearances were normal except for minute RPE disturbance in one case and temporal pallor of the optic disk in one case. AF imaging was normal in three cases but slight hyper AF at the fovea/parafovea was observed in three/two cases. OCT revealed disappearance of the interdigitation zone and blurred ellipsoid zone (EZ) in the posterior pole region in all the cases; however, foveal EZ was spared in three cases. Full-field ERG showed severely reduced cone responses in five cases and moderately reduced cone responses in three cases. Rod responses were normal in all the cases. Multifocal ERG showed preserved central responses in two cases. The clinical diagnosis was either generalized cone dystrophy in twelve eyes of seven cases or cone dystrophy with foveal sparing, i.e., peripheral cone dystrophy, in four eyes of three cases.

Conclusions: Generalized or peripheral cone dystrophy with normal fundus appearance is thought to be a representative phenotype of POC1B-related retinopathy. The characteristic morphological changes in photoreceptors with preserved retinal pigment epithelium coincide with other ciliopathies such as RP1L1-associated retinopathy.

1.05 Monitoring the development and treatment of suspected choroidal neovascularization in Best vitelliform macular dystrophy with OCT angiography and visual electrophysiology in pediatric patients

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Purpose: To monitor retinal function and vascular changes using visual electrophysiology and optical coherence tomography angiography (OCTA) in pediatric patients and their affected family members diagnosed with juvenile-onset Best disease.

Methods: Ten pediatric patients (ranging in age from 2 to 16 years) and three adult patients (ranging from 23 to 51 years old) with Best vitelliform macular dystrophy underwent a standard ophthalmic examination including eye fundus photography, OCT and OCTA imaging, as well as fERG and mfERG when possible. Patients presented either with active choroidal neovascularization (CNV) (suspected CNV, n=2 eyes), inactive CNV (post-anti-VEGF treatment, n=4 eyes) or non neovascular (non CNV, n=20 eyes)

forms of Best disease. Two pediatric patients with suspicion of CNV (10 and 16 years old) presented with a history of sudden decrease in vision in one eye and were treated with unilateral intravitreal bevacizumab (IVB) injections (1.25 mg/0.05 ml). Both patients had testing performed before and after treatment.

Results: Retinal function analysis showed normal photopic ERGs in all patients, while scotopic mixed ERG amplitudes were reduced in four patients (by 50-60%, $p<.05$; active and inactive groups only). mfERG amplitude attenuation was limited to ring 1 and to rings 1-2 in all pediatric and adult patients, respectively. Interestingly, in the non neovascular group, despite being clinically asymptomatic (VA=20/20), significantly lower foveal amplitudes (by 40-50%; $p<.05$) were still noted in 4 children. OCTA analysis revealed vascular abnormalities of different degrees and patterns, ranging from dispersed to dense ring-shaped patches of vessels mostly at the deep and choriocapillaris level, changes present even in patients with VA of 20/20. Blood flow analysis showed positive flow signals corresponding to these neovascular networks in some cases, findings suggestive of early CNV. In general, adults showed less obvious vascular changes than children. Following IVB injections, the two treated patients showed improvement in their VA from 20/100 and 20/400 to 20/70 and 20/60, respectively, which was accompanied by an increase in mfERG response amplitude. In addition, in the first 10-year-old patient, significant vascular regression occurred on OCTA (i.e. from a dense ring-shaped vascular network covering almost the entire foveal avascular zone to few sparsely scattered vessels). Interestingly, no significant vascular abnormalities were observed in the second patient despite significant VA fluctuations.

Conclusions: The vitelliform nature of lesions makes detection and follow up of CNV challenging in Best disease, particularly in the pediatric population. Our results show that OCTA is not only an excellent follow-up modality for assessing disease progression and treatment response, it can also be successfully obtained in children as young as 2 years old. Combined with the mfERG, both appear to be efficient in identifying functional (i.e. mfERG amplitude reduction) and vascular (i.e. early signs of CNV) changes prior to any visual complaint, knowledge that is crucial for rapid therapeutic intervention to limit any potential macular damage. Interestingly however, in some cases, as seen with our second treated patient (i.e. normal OCTA, but abnormal mfERG), the mfERG might be more sensitive to detect subtle retinal impairments than the OCTA.

Funding: FROUM

1.06 Riggs-type dominant congenital stationary night blindness with a systemic association and a new GNAT1 mutation

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Purpose: Complete congenital stationary night blindness (CSNB) is most often associated with a transmission defect from photoreceptors to bipolar cells, which produces a characteristic Schubert-Borschein "negative" scotopic ERG. CSNB from phototransduction abnormalities are much less common and produce a Riggs-type of ERG with no rod a-wave. We analyzed the clinical findings and genetics of a Chinese father and daughter with Riggs-type CSNB and an associated autonomic abnormality, postural orthostatic tachycardia syndrome (POST).

Methods: Standard clinical examination and imaging were performed. ERGs were recorded with an Espion unit, following the latest ISCEV standards. Initial gene testing by Blueprint Genetics was supplemented with Sanger sequencing and 3-D modelling of the domain.

Results: Both father and daughter had good acuity and mildly myopic fundi without retinal degeneration. The scotopic ERGs showed no rod response, but there was a small rapid signal that appears to be generated by the cones. The cone responses were unremarkable. Both patients showed a novel variant (c.155T>A p.Ile52Asn) in GNAT1 coding for the α-subunit of transducin. 3D-modeling suggested that this variant does not affect the GTP binding-site as do other dominant CSNB GNAT1 mutations, and may have a new mode of action. The retinal gene panel did not reveal any known abnormalities that might account for the association with POST.

Concusions: This family shows the third known autosomal dominant GNAT1 abnormality in complete CSNB and may reveal a new pathogenic mechanism within the gene. POST is not typically an inherited disorder, and the only dominant gene reported in a family was on a different chromosome. The presence of POST in our two patients remains a puzzle. These cases illustrate the clinical and Riggs-type ERG findings that characterize CSNB with a defect in phototransduction.

Wednesday 20th June 2018, 10:30–11:45

Session 2: Paper Session — Methods & Innovations I

2.01 Peripheral PERG (pPERG) high-frequency response components in normally sighted and glaucomatous eyes

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Purpose: Conventional pattern electroretinogram (PERG) response waveforms include three prominent components, N35, P50, and N95 and are generated by the central retina. A recently introduced PERG stimulus source stimulates the peripheral retina; the peripheral PERG (pPERG) response waveforms include two prominent components similar to P50 and N95 but with shorter implicit times, plus three high-frequency components (F1, F2 and F3) that are well-isolated with a passband of 50-1000 Hz. The amplitudes and implicit times of the high-frequency components were evaluated in normally-sighted subjects and in glaucoma patients, to determine if these response components are affected in glaucoma.

Methods: The PERG stimulus consisted of four circumferential rows and 30 radial columns of approximately ten degree checks arranged on a hemispherical surface located 30 cm from the eye. The stimulus field subtended 35-85 degrees from fixation and mean ON-luminance was 1670

photopic cd/m^2. Study participants included early and mid-stage glaucoma patients (n=12) and normally-sighted subjects (n=11). All study participants were selected based on visual field results (24-2 protocol) and circumpapillary retinal nerve fiber layer thickness (Heidelberg Spectralis). For each participant, responses to approximately 300 pattern reversals were recorded (passband 1-1000 Hz) and averaged for analysis. The pPERG response waveforms were passed through a zero-phase-shift 8th order Butterworth filter with passband 50-1000 Hz to isolate the high-frequency response components, named F1, F2, and F3. The three high-frequency components were evaluated for amplitude and implicit time, yielding six feature values for each participant. Student's unpaired t-test was used to compare values for each feature between the normally-sighted subjects and glaucoma patients.

Results: The high-frequency positive peaks occurred at approximately 21, 29, and 38 ms for F1, F2, and F3, respectively, in normally-sighted subjects. For F1 and F2, glaucoma patients had, on average, longer implicit times (p = 0.009, 0.037, respectively). Average amplitudes were approximately 3.0, 2.6 and 2.7 μV, for F1, F2, and F3, respectively, in normally-sighted subjects. For F1 and F3, glaucoma patients had, on average, reduced amplitudes (p=0.005, 0.016, respectively). F3 implicit times and F2 amplitudes were not significantly different, on average, between normally-sighted subjects and glaucoma patients (p=0.265 and 0.273, respectively).

Conclusions: The high-frequency response components observed in the pPERG waveform may have diagnostic value in glaucoma. These components are robust, with very consistent implicit times. High-frequency components are not observed in conventional PERG, largely due to the low-pass filtering effect of progressive scan displays used to present the stimulus; the PERG responses reported here were evoked with a synchronously updated stimulus (i.e. entire pattern reverses at the same time).

2.02 A battery of short-duration VEP tests for assessment of traumatic brain injury

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Purpose: To introduce a battery of short-duration VEP tests that can assess a range of neural functions possibly affected in cases of head trauma through implementation of appropriate visual stimuli and objective frequency-domain analyses of responses.

Methods: Previously, we developed several rapid VEP techniques that tap select visual pathways and mechanisms. Frequency-domain measures were computed to quantify the responses objectively, along with tests of statistical significance. In the current work, we applied this battery of VEP tests to a group of veterans who returned from conflicts in Afghanistan/Iraq (n=11 males, age range: 22-39) and compared their responses to a group of healthy observers (n=89, age range: 17-47 years, 46 males). Six of the veterans self-reported traumatic brain injury (TBI) or posttraumatic stress disorder (PTSD), both of which have been associated with blast injuries in this population. The battery included the following tests of 10 runs each: short-duration transient VEPs (tVEPs) to a 1-Hz contrast-reversing 32x32 checkerboard of high contrast (2-s EEG epochs/run); steady-state VEPs (ssVEPs) to contrast sweeps of bright or dark isolated-checks which drive ON or OFF pathways, respectively (6-s epochs/run); ssVEPs to spatial frequency sweeps of horizontal gratings (6-s epochs/run) which yield estimates of grating acuity; ssVEPs to radial stimuli (partial-windmill, windmill-dartboard, two-sinusoid dartboard, 2-s epochs/run) to examine lateral inhibitory processes and high-frequency input to visual cortex. Data collection was synchronized to the frame rate of a CRT display (150 frames/s, 10°x10° field). All observers had 20/25 visual acuity or better with correction at the viewing distance of 114 cm. A discrete Fourier transform was applied to obtain harmonic frequency components up to 100 Hz, Tcirc2 and magnitude-squared coherence (MSC) statistics were computed for each relevant harmonic component to obtain signal-to-noise ratios and test for statistical significance. Amplitude, phase, and power were computed for each harmonic. Distinct frequency mechanisms identified by means of principal component analysis were measured with MSC and power statistics, and phase-derived time delays were

calculated. Comparisons were made to conventional tVEP time-domain measures.

Results: Veterans overall exhibited deficits on an array of functions compared to healthy controls. Those with neurologic complaints (TBI/PTSD) demonstrated select dysfunction that is specific to the individual. Some functions remained intact in veterans: grating acuity, lateral interactions, and the high region of contrast response functions. Novel frequency-domain measures of tVEPs were particularly sensitive to loss of function in these cases: MSC and power in a frequency band (14-28 Hz) found to yield the key features of the tVEP waveform.

Conclusions: The VEP battery used in this study, which applies objective and statistically rigorous frequency-domain measures, tests a wide range of neural functions; thus, it is capable of profiling deficits in veterans exposed to combat. Validation with a larger and more diverse sample of individuals with brain injuries remains for future work.

2.03 Investigation of scotopic vision with mfVEPs

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Purpose: Photopic multifocal visual evoked potentials (ph_mfVEPs) allow for objective visual field testing (Herbik et al. *Ophthalmic Physiol Opt* 2014;34:540-51). In contrast, the scope of scotopic mfVEPs (sc_mfVEPs) remains unexplored. To fill this gap, we investigated the sc_mfVEPs potential and aimed to detect the central scotoma and increased response latencies typical of scotopic vision.

Methods: In nine participants, ph_mfVEPs (mean luminance=103 cd/m2, contrast=95%) and sc_mfVEPs (0.003 cd/m2; 30 min dark adaptation) were recorded for 36 visual field locations of a circular checkerboard pattern (25° radius) and analyzed in an eccentricity dependent manner. Latency shifts between ph_mfVEPs and sc_mfVEPs were determined with cross correlations. Signal-to-noise ratios (SNR) (Hood et al. *Prog Retin Eye Res* 2003;22:201-51) were compared between two time windows, one for photopic (phTW) the other for scotopic (scTW) response latency.

Results: Sc_mfVEPs were delayed by 97 ms compared to ph_mfVEPs. For the phTW sc_mfVEP-SNRs were less than half of the ph_VEP-SNRs. For the scTW sc_mfVEP SNRs were only centrally reduced (by 81% foveally and by 29% parafoveally); peripherally they were increased by up to 3% compared to ph_VEP-SNRs.

Conclusions: Sc_mfVEPs were delayed compared to ph_mfVEPs and demonstrated the central scotoma typical of scotopic vision. This provides proof-of-concept of the sc_mfVEP. Consequently, sc_mfVEPs have the potential for an objective visual function test in patients with ophthalmologic diseases specifically impairing scotopic vision.

2.04 Portable device for VEP monitoring I. Technical parameters and VEP characteristics

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Purpose: We present the latest results of our efforts to develop a mobile and simply usable device for VEP examination at various locations (e.g. at patient bedside, at home).

Methods: The novel low-cost wearable device mounted in a headset carrier consists of a visual stimulator (a matrix of 32 light-emitting diodes with adjustable luminance and colour), producing a large spectrum of monocular or binocular stimuli (including those with a cognitive task) and a recording part (based on a 4-channel EEG amplifier). Two dry electrodes (not requiring any skin preparation), placed in a fixating belt of the headset, record VEPs from the forehead (about Fp1 and Fp2 locations) and two additional standard Ag-AgCl electrodes can be freely located over the activated parts of the brain cortex (according to the used variant of visual stimuli).

The ergonomic headset enables positioning of the visual stimuli in various parts of the visual field. The recorded VEPs are transmitted, via a USB port, to a PC for display and off-line evaluation. The device is supplied with a sensor of the background luminance (influencing the LED stimulation luminance) and with a 3D accelerometer serving to eliminate artefacts caused by movements of subjects during examinations. Long-term monitoring of VEPs is desirable for certain patients (even during working activities). Easy handling of the device eliminates need for specialised staff and also allows self-examination.

Results: With the described variant of the portable VEP device, we have so far tested responses of healthy subjects and neuro-ophthalmological patients to the following stimuli:

- Simulation of black-white pattern-reversal with low spatial frequency of 0.12 c/deg (determined by the size of the used LEDs) providing the standard P100 dominant peak at Oz location.

- Flash stimulation 1 Hz producing standard cortical flash VEPs in all used electrodes and ERG activity in Fp1 and Fp2 (dominant on the side of the stimulated eye).

- Red-green flicker with frequency of 1 Hz generating the largest VEP response in the majority of subjects with dominating positivity at about 110 ms in Oz and Pz electrodes.

- Motion-onset stimulation with 200 ms motions (and 1 s interstimulus interval) of LED triplets changing direction in the horizontal axis. This stimulus produced standard motion-onset negativity at about 160 ms, which was well seen also in prefrontal areas in the majority of subjects.

Conclusions: We believe that our portable device is about ready for larger (international) testing of its diagnostic possibilities and it is the reason why we present it at the ISCEV meeting. We hope it will not follow the lines of the motion-onset VEPs that have not as yet attracted major attention of the ISCEV community and VEP devices manufacturers.

Funding: Charles University - project PROGRES Q40/07

2.05 Portable device for VEP monitoring II. Live demonstration of VEP examination

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Purpose: To present properties and possibilities of the portable device, we will use a live demonstration with the following scenarios: 1. Recording of ERG from Fp1 and Fp2: Luminance changes will evoke the photopic flash ERG. 2. Recording of VEPs: Color, monochromatic and motion stimuli without luminance changes will evoke cortical responses from occipital and parietal areas predominantly. 3. Recording of ERPs based on multiple triggering and oddball paradigm together with reaction time measuring.

Methods: Basic technical data of the device and characteristics of the recorded VEPs are specified in the abstract of the first part of our presentation. There have been some limiting problems in the use of the portable device. For obtaining “pattern-reversal VEPs” with higher spatial frequency, comparable with standard examination, it will be necessary to replace the stimulus part of the device with a high-density OLED display. The short viewing distance (7 cm between eyes and the stimulus field) would require incorporation of some optic component for better focusing. In some individuals there is a significant difference in the recorded VEPs from Oz dependent on vertical changes of the fixation point (related to the topography of the upper and lower visual half-field in the striate cortex). The good quality of low noise amplifiers high efficiency of the selected stimuli, on-line elimination of artefacts and Sawitzky-Golay smoothing of the signal allow acquisition of averaged VEPs (with sufficient signal-to noise ratio) from only 20 single sweeps, which also leads to significant shortening of VEP examinations.

Results: Robust reliable VEPs can be recorded in over 90% of subjects. In some cases (severe involvement of the visual pathway), the used stimuli evoke reactions despite missing VEPs in standard examination. Since we use non-standard types of visual stimulation, it has been quite difficult to make a proper interpretation of the new findings without detailed knowledge of normal characteristics of the new VEPs. VEPs from the prefrontal electrodes can be recorded mainly with the use of peripheral flash or motion stimuli. They might provide useful information in the case

of self-examination, since these built-in dry electrodes do not require any preparation. We succeeded to prove that with the portable device there is a good chance to perform a basic VEP examination even in babies at intensive care units, which can provide valuable information about the CNS and visual function.

Conclusions: The demonstrated portable VEP device could represent a needed variant of the basic VEP examination outside specialized labs for a screening of visual pathway and CNS dysfunction and long-term monitoring of VEP changes. We would like to offer prototypes of the device to interested labs for its multicenter testing with the aim of expanding the diagnostic use of VEPs.

Funding: Charles University - project PROGRES Q40/07

Wednesday 20th June 2018, 13:15–15:15

Session 3: Poster Session 1

3.01 The usefulness of visual electrophysiology in pendular nystagmus in infancy

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Purpose: Strictly pendular nystagmus in infancy, partially or completely overlapping with so-called spasmus nutans-type nystagmus, has long been considered a benign entity. It is now a well-recognised symptom of various neurological or retinal diseases. In this study we looked at the place and usefulness of visual electrophysiology in the etiological work-up of pendular nystagmus in infancy.

Methods: All cases of infants presenting to our institution nystagmus clinic with a strictly pendular nystagmus between 2010 and 2016 were included. Cerebral imaging and visual electrophysiology were performed. Infants with a causal diagnosis known before the first nystagmus clinic appointment were excluded.

Results: Fifty infants (34 boys, median age at nystagmus onset: 6 months) were included. MRI showed a large chiasmal glioma in 10 cases (20%), a leukoencephalopathy in five cases (10%), and a significant malformation in three cases (6%). Visual electrophysiology was obtained in 44 cases (88%). ISCEV full-field ERG allowed diagnosis of 19 cases (38%) with retinal dysfunction: early-onset severe retinal dystrophy (nine cases, two of which also exhibited dysmyelination), stationary cone dysfunction (eight cases), and congenital stationary night blindness (two cases).

Conclusions: In 70% of cases, pendular nystagmus was associated with a retinal or neurological disorder. Visual electrophysiology was the key exam for diagnosing a retinal disorder. Unless a chiasmal glioma is found on MRI, a full-field ERG should be part of the work-up of pendular nystagmus in an infant, including in the presence of leukoencephalopathy.

3.02 Comparison of RETeval and OCT findings in glaucoma patients

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Purpose: To determine the relationships between the morphology of the optic disc, retinal nerve fiber layer (RNFL) thickness, macular ganglion cell complex (GCC) thickness, and the photopic negative responses (PhNR) recorded by the RETeval™ system in glaucoma patients.

Methods: Fifty eyes of 50 glaucoma patients [average age 68.7 years; average visual field mean deviation (MD) -11.28 dB (range, +0.62 to -29.34 dB)] were studied. The RETeval™ Complete system with a non-mydriatic PhNR 3.4 Hz Td mode was

used, and the PhNR-related parameters, viz., the P72 amplitude, Pmin amplitude, Pmin implicit time, P ratio (P72 amplitude/b-wave), and W ratio [(b-wave - Pmin amplitude)/(b-wave – a-wave)] were evaluated. The RS-3000 Advance OCT (NIDEK Co.) was used to evaluate the morphology of the optic disc and inner layer of the macula. For the optic disc, the vertical cup/disc (C/D) ratio, average peripapillary RNFL thickness (RNFLT), and macular GCC thickness (average macular thickness over 9 mm in diameter) were used. The relationships between the values of the OCT parameters and the values of each PhNR-related parameter of the ERGs obtained by the RETeval™ system were determined.

Results: The highest significant correlation was found between the W ratio of the PhNR and the RNFLT ($r=0.74$, $p<0.01$). Other high correlation coefficients were detected for the Pmin amplitude and the RNFLT ($r=-0.62$, $p<0.01$), the P72 amplitude and the RNFLT ($r= 0.60$, $p<0.01$), the W ratio and the GCC thickness ($r=0.59$, $p<0.01$), and the W ratio and the vertical C/D ratio ($r=-0.55$, $p<0.01$). There were also significant correlations among the W ratio, P72 amplitude, P ratio, Pmin amplitude, and the OCT parameters (all $p<0.01$), but there were no significant correlations between the Pmin implicit time and OCT parameters (all $p>0.05$).

Conclusions: The moderate to strong correlations between the PhNR parameters, excluding the Pmin implicit time, recorded by the RETeval™ system and the OCT parameters suggest that analyses of the PhNR by the RETeval™ system are practical methods for detecting inner retinal dysfunction and structural changes in glaucoma patients.

3.03 Advanced analysis of PERG signals in early primary open-angle glaucoma

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Purpose: To evaluate discrete wavelet transform coefficients and identify descriptors of pattern electroretinogram (PERG) waveforms in order to determine PERG characteristics for optimizing the diagnosis of early primary open-angle glaucoma (POAG).

Methods: PERG were recorded according to ISCEV protocol for 30 normal eyes and 30 POAG eyes using 0.8° and 16° black and white checks. Results were analyzed in time domain (TD) and discrete wavelet transforms (DWT). DWT descriptors were extracted at levels 6 and 7 of Daubechies 4 (db4), Daubechies 8 (db8), Symlet5 (sym5), Symlet7 (sym7), and Coiflet5 (coif5) wavelets. Signals were reconstructed by inverse DWT. All data obtained by TD and DWT analyses were compared between the two groups.

Results: For both check sizes, a significant attenuation of N95 amplitude was seen in the patient group. For 0.8° checks, N95 descriptor (7N) of db8 had the highest value and showed a significant increase as compared to the POAG group. For 16º checks, there was no significant difference between groups. A strong correlation was seen between reconstructed signals and originals ($r = 0.99$).

Conclusions: The DWT can quantify PERG responses more accurately. In agreement with TD and wavelet coefficients domain results, 7N of db8 decomposition can be used as a good indicator for early detection of POAG.

3.04 Discrete wavelet transform of pattern reversal VEPs in anisometropic amblyopia versus normal eyes

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Purpose: To extract new descriptor of pattern reversal visual evoked potential (prVEP) waveforms for optimizing the stimuli in the diagnosis of anisometropia amblyopia.

Methods: prVEPs were obtained from 31 normal eyes and 35 amblyopic eyes. The stimuli consisted of spatial frequencies of 1, 2, and 4 cycles per degree (cpd) and contrast levels of 100%, 50%, 25%, and 5%. Results were analyzed in time and time-frequency domains. DWT descriptors were extracted at level 7 (7P descriptor) of Haar (haar), Daubechies 2 (db2), Daubechies 4 (db4), Symlet 5 (sym5), Biorthogonal 3.5 (bior3.5), Biorthogonal 4.4 (bior4.4), and Coiflet 5 (coif5) wavelets for 12 stimuli and compared between the two groups. Correlation between different spatial frequencies at the same contrast level as well as similarities between reconstructed signals and VEP waveforms were evaluated.

Results: P100 amplitude showed significant reduction and latency increased dramatically in the patient group. In the amblyopic group, 7P descriptor decreased in all analyses, except at a spatial-frequency of 7cpd and contrast of 5% using bior4.4. A weak correlation was seen between different frequencies at a special contrast and a strong correlation was seen between reconstructed signals and originals.

Conclusions: The 7P descriptor can be used for differentiating normal and abnormal signals in anisometropia amblyopia. Our findings showed that the DWT using coif5, db4, bior4.4, and bior3.5 wavelets can be utilized as a good indicator for selecting optimum stimuli.

3.05 Newly defined N95 amplitude in the PERG

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Purpose: To investigate the utility of selected pattern electroretinogram (PERG) parameters—including conventional N95 amplitude and N95/P50 ratio, and a newly defined N95 amplitude—in the analysis of visual function(s) and for predicting changes in retinal ganglion cell structure in optic neuropathies.

Methods: This retrospective, observational case series was performed at a single center. Forty-four eyes from 36 patients diagnosed with optic neuropathy were included. A new N95 amplitude was defined as the amplitude measured from baseline to the trough of N95. PERG and pattern visual evoked potential (PVEP) measures were acquired within 1 week after onset of optic neuropathies. To compare functional and anatomical changes, mean temporal peripapillary retinal nerve fiber layer (pRNFL) and average and minimum ganglion cell-inner plexiform layer (GC-IPL) thicknesses were measured using optical coherence tomography (OCT).

Results: Thirty-six patients (20 male, 16 female; mean age 37.5±17.6 years) were evaluated. The new N95 amplitude was significantly smaller than the conventional N95 amplitude (1.0±0.56 μV and 2.45±1.02 μV, respectively; $p<0.0001$). Both the N95 and new N95 amplitudes were significantly correlated with visual acuity ($r=-0.38$, $p=0.010$ and $r=-0.32$, $p=0.029$, respectively). Although P100 latency was not correlated with all PERG parameters, the N95 and new N95 amplitudes demonstrated a positive correlation with P100 amplitude in PVEP ($r=0.32$, $p=0.032$ and $r=0.41$, $p=0.005$, respectively). PERG parameters, including the N95 and new N95 amplitudes and N95/P50 ratio, were not correlated with pRNFL thickness in OCT. Only the new N95 amplitude demonstrated a significant correlation with GC-IPL.

Conclusions: The new N95 amplitude, measured from baseline to the trough of N95, was valuable in the analysis of visual function(s) and for predicting changes in retinal ganglion cell structures in optic neuropathies.

3.06 Natural course of chronic non-arteritic anterior ischemic optic neuropathy: pattern electroretinography review

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Purpose: To evaluate the natural course of chronic phase non-arteritic anterior ischemic optic neuropathy (NAION) in terms of pattern electroretinography, retinal ganglion cell (RGC) thickness and visual field defect.

Methods: Prospective evaluation of chronic phase NAION was performed in 23 eyes of 17 patients (11 unilateral NAION and 6 bilateral NAION). The examinations were performed >6 weeks after onset and at 1 month and two months after initial examination. Examinations included pattern electroretinography, optical coherence tomography panomap and Humphrey visual fields.

Results: The first visits were performed at 24 (12-104) weeks after onset. There was an increase of P50 and N95 amplitude observed in 23 eyes of chronic phase NAION over the three measurement times [(P50=4.839±1.921 μV; 5.291±2.256 μV; 5.622±2.377 μV (p=0.008); N95=-4.304±1.224 μV; -5.574±3.296 μV; -6.213±2.956 μV (p=0.01)]. There were no statistically significant differences in implicit time as a function of visit. Compared to normal fellow eyes, NAION eyes showed significantly lower P50 and N95 amplitudes ($p<0.05$). The RGC thickness showed a stable atrophic state without significant change over the three measurements (p=0.406). Visual field defect also showed no significant change over time (p=0.304). No correlation was found among P50-N95 amplitude and mean deviation or pattern specific deviation. There was a significant correlation between P50 amplitude at first visit with RGC thickness at third visit (r=-0.558, p=0.02) and N95 amplitude at first visit with RGC thickness at third visit (r=0.519, p=0.033). There was no significant correlation between mean deviation-pattern specific deviation and RGC thickness.

Conclusions: Contrary to the conventional belief, chronic-phase NAION showed a change of P50 and N95 amplitude over time, suggesting the possibility of improving retinal ganglion cell function although its thickness and the visual field defect had stabilized. P50 and N95 amplitude showed a different pattern in unilateral NAION and correlated with final retinal ganglion cells thickness.

3.07 PERG in the assessment of the risk of glaucoma conversion in patients with OHT in five-year follow-up

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Purpose: Estimation of the value of the PERG in predicting the risk of conversion of ocular hypertension (OHT) to glaucoma during a five-year follow-up.

Methods: In 100 eyes from 50 OHT patients (mean age 48±13 years), PERG was performed according to a methodology described by Parisi et al. (*Ophthalmology* 2006;113:216-228). Patient characteristics included mean intraocular pressure 26±3.0 mmHg; PS-24-2 (W-W), "Full Threshold", Mean Deviation (MD) >-2.0 dB; and normal retinal nerve layer by optical coherence tomography. Measured parameters were P50 and N95 wave amplitude, N95 to P50 wave amplitude ratio (AN95/AP50), and P50 implicit time. After 5 years, the rate of OHT conversion to glaucoma was assessed, and correlations between the baseline parameters of PERG and the stage of glaucoma neuropathy were determined. The results were statistically calculated using the significance level $p<0.05$.

Results: Initial abnormalities in PERG were seen in 32 eyes of 16 OHT patients (32%). The most common abnormality was decreased AN95/AP50 ratio. After 5 years, glaucoma, according to European Glaucoma Society criteria, was observed in 24 eyes (24%) - 18 eyes (56%/10 patients) with baseline abnormal ganglion cell function in the PERG and 6 eyes (9%/four patients) with normal baseline function, $p<0.0001$). A significant correlation between the MD and PSD parameters of static perimetry and the initial PERG values was also demonstrated.

Conclusions: The PERG is useful in identifying patients with ocular hypertension at risk of conversion to glaucoma.

3.08 Normal values of standard full-field ERGs and VEPs in Indonesian adults

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Purpose: Following the ISCEV recommendation that each laboratory should have its own normal values for full-field electroretinography (ffERG) and visual evoked potential (VEP), the purpose of this study is to establish normal values for an Indonesian adult population, using the Metrovision system, that will be applied for our new laboratory.

Methods: Fifty-eight normal eyes from Indonesian subjects, ranging in age from 19 to 49 years, were tested. ERG amplitude and implicit time and VEP amplitude and latency were measured according to ISCEV recommendations. ERGs were recorded using a Dencott contact lens electrode. ERG evaluations consisted of scotopic 0.01, 3.0, and 3.0 oscillatory potentials and photopic 3.0 and 30 Hz flicker. VEP recording was done using 15' and 60' checks.

Results: Mean scotopic 0.01 b-wave amplitude was 285 ± 76 µV and b-wave implicit time was 77 ± 7 ms. Mean scotopic 3.0 a-wave amplitude was -285±55 µV, a-wave implicit time was 24±1 ms, b-wave amplitude was 297±133 µV, and b-wave implicit time was 46±3 ms. Mean scotopic 3.0 OP-wave sum amplitude was 343±124 µV and OP1-wave implicit time was 21±1 ms. Mean photopic 3.0 flicker b-wave amplitude was 46±41 µV and b-wave implicit time was 29±2 ms. For the VEP, latency was 108.0±5.9 ms in male subjects and 107.4±5.4 ms in females. Amplitude was 14.0 µV in males and 18.7 µV in females.

Conclusions: Our results may serve as a reference for normal values of standard ffERG using a Dencott electrode and pattern VEP in an Indonesian adult population.

3.09 The effect of age on ISCEV standard ERGs recorded with skin electrodes

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Purpose: To evaluate the effect of age on ISCEV standard ERG recorded with skin electrodes.

Methods: ERGs were recorded using skin electrodes from 77 normal subjects ranging in age from 9 to 86 years. A pulse reference power line noise reduction system (PuREC, Mayo, Nagoya, Japan) was used. Linear regression analysis against age was performed on the amplitude and the implicit time of each component.

Results: The amplitude and implicit time of each component were as follows (mean ± SD, p value, and r value); Dark-adapted (DA) 0.01 ERG: 56.1±16.0 µV (p=0.018, r=0.269), 87.5±10.6 ms (p=0.011, r=0.287); DA 3 ERG a-wave: 59.3±15.2 µV (p=0.006, r=0.313), 19.9±2.6 ms (p<0.001, r=0.465); DA 3 ERG b-wave: 91.5±23.2 µV (p=0.049, r=0.224), 50.3±6.9 ms (p=0.018, r=0.269); Light-adapted (LA) 3 ERG a-wave: 8.1±2.1 µV (p=0.005, r=0.330), 17.1±1.0 ms (p=0.022, r=0.270); LA 3 ERG b-wave: 35.9±10.7 µV (p<0.001, r=0.386), 31.4±1.3 ms (p<0.001, r=0.449); flicker ERG: 31.1±8.7 µV (p=0.049, r=0.256), 28.7±1.7 ms (p=0.003, r=0.383), respectively.

Conclusions: Significant age dependence was found for the amplitude and the implicit time of each ERG component recorded with skin electrodes.

3.10 Visual electrophysiology development from infant to teenager in Western China

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Purpose: To investigate the development of visual electrophysiology parameters from normal infants to teenagers, enabling precise diagnosis for age-matched patients.

Methods: We performed a retrospective analysis of the visual electrophysiology results of normal eyes in subjects ranging from infants to teenagers.

The normal eye from individuals whose other eye was accidentally injured was evaluated. We analysed full-field ERG (ffERG) response amplitude [dark-adapted (DA) 0.01, 3.0, and 10.0, light-adapted (LA) 3.0 and 30 Hz flicker], PERG P50 and N95 amplitude and P50 peak time, pattern VEP (prVEP) P100 amplitude and peak time, and flash VEP (FVEP) P2 peak time. Also, each response component was plotted against age to see the developmental trend. Tests were performed using Diagnosys system following ISCEV standards.

Results: For ffERG (24 eyes), amplitude of each wave of one 3 year-old infant were: DA 0.01 b-wave: 268 µv; DA 3.0 a-wave: 244 µv, b-wave: 536 µv; OP2: 52 µv; DA 10.0 a-wave: 332 µv, b-wave: 536 µv; LA 3.0 a-wave: 54µv, b-wave: 145µv; flicker: 127µv. Amplitude of each response reached adult level at 3 years of age. Ranges of PERG P50 amplitude, peak time, and N95 amplitude from 4 to 18 years-old (19 eyes) were close to the adult range (P50: 6.4±1.2 µv, 48.8± 3.3 ms; N95: 0.2 ±1.9 µv). For prVEP (56 eyes), peak time was constant with age (1° checks: 98.3±4.45 ms; normal control was 98.3±3.3 ms), while amplitude reached its highest high level at age 8-12 years and then decreased slowly to adult level at about age 18. For FVEP (32 eye), peak time remained in the same range as that of adults (from 72 to 126 ms)

Conclusions: In this study, ffERG reached nearly adult level at about 3 years of age. PERG P50, N95 amplitude and P50 peak time reached nearly adult level at 4 years of age (in cases when it can be recorded). PrVEP P100 amplitude increased with age until 8 to 12 years, then decreased to adult level at about 18 years; peak time stayed constant with age. FVEP P2 peak time stayed close to the normal adult range.

3.11 Comparison of two color vision tests in patients with Leber's hereditary optic neuropathy

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Purpose: The aim of this work was to compare two color vision tests to measure chromatic discrimination in Leber's hereditary optic neuropathy (LHON) patients treated by gene therapy: color contrast sensitivity test (measured by the Cambridge Colour Test) and the Farnsworth Standard D15.

Methods: For this study, we selected 24 patients (48 eyes), age 16-73 years (mean 42.5 ±14.3), diagnosed with a LHON (mutation ND4-11778). We assessed on the same day the best corrected visual acuity using the ETDRS chart and performed the Farnsworth Standard D15 and the Cambridge Colour Test.

Results: In order to evaluate the concordance between the Cambridge Colour Test and the Farnsworth Standard D15, we used a statistical analysis to calculate the Gwet's coefficient AC1. We found a highly significant correlation between the two tests as evidenced by the coefficient of 0.80 (95% CI 0.65 - 0.95).

Conclusions: This study demonstrated a concordance between the most commonly used color vision test, the Farnsworth Standard D15, and the color contrast sensitivity test that is claimed to be more reliable and accurate by quantifying the potential for discrimination on each chromatic axis.

3.12 No light perception but existing P2 wave in flash VEP of optic neuritis patient: case report

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The patient was a 16 year-old female who had been previously diagnosed with optic neuritis at another hospital in 2013, was treated with corticosteroid, and became better.

May 18th, 2018. Right eye: Visual acuity was reduced for 4 days without obvious etiology. Corrected visual acuity (VA) was 0.02. IOP was 16.2 mmHg. Pupil diameter was 8 mm with regular shape, loss of direct pupillary light reflex, and weak indirect pupillary light reflex; RAPD (+). Left eye was normal and VA was 1.2.

Initial diagnosis: Optic neuritis due to demyelination, nerve atrophy.

May 19th, 2018. VA of right eye was no light perception and that of left eye was 1.0. Flash VEP (FVEP) was tested and P2 wave was detected with stimulation of either eye. Full-field ERG was normal. OCT showed RNFL thickness thinned at each quadrant; C/D was 0.36. FFA showed normal A-RCT(11s), obvious optic disc border, larger optic cup, and weak fluorescence.

Treatment: Right eye improved after corticosteroid treatment, blood circulation-improving treatment, and neurotrophic treatment.

May 27th, 2018. Right eye: VA was 0.02; localization of a light source was precise in all directions. IOP was 16.2mm Hg. Pupil was regular with diameter of 3mm and reactive pupil light reflex. Optic disc pallor and clear border were noted; c/d ratio was 0.3, with regular blood vessels. Left eye was normal and VA was 1.2.

Conclusions: P2 of the FVEP may not disappear in an eye with loss of light perception.

3.13 Atypical presentation of palinopsia

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Purpose: Isolated ophthalmological involvement in progressive multifocal leukoencephalopathy is uncommon. Visual evoked potentials can help in the diagnosis of retrochiasmal dysfunction.

Methods: This is an observational and descriptive case report.

Results: A 67 year-old male patient with a history of myasthenia gravis diagnosed thirteen years ago and treated with monoclonal anti-CD20 (Rituximab) was referred for mild bilateral visual loss associated with palinopsia. Visual acuity was 5/10 in the right eye and 9/10 in the left eye. Slit lamp and neurologic examinations were normal. Optical coherence tomography was also normal. Automated visual field validated bilateral central scotoma. Pattern electroretinogram was normal. Visual evoked potentials demonstrated uncrossed asymmetry of lateral electrodes distribution over the posterior scalp, related to retrochiasmal dysfunction. Cerebral MRI showed bilateral white matter lesions without mass effects in the parieto-occipital lobes. Brain biopsy confirmed the diagnosis of progressive multifocal leukoencephalopathy.

Conclusions: We report uncrossed asymmetry of visual evoked potentials, revealing progressive multifocal leukoencephalopathy related to rare immunosuppressive therapy (Rituximab).

3.14 Bilateral optic neuropathy confirmed with VEPs in a case of chronic chrome/cobalt intoxication

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Purpose: Optic neuropathy is a common condition in daily practice and diagnosis often remains difficult due to multiple nosologic contexts. Toxic optic neuropathy is a common cause of bilateral, progressive visual loss associated with a normal optic disc appearance at early stages and a caeco-central defect on the visual field. For the diagnosis of toxic optic neuropathy, a thorough investigation is required to finally lead to the identification of the causal agent.

Methods: We report the case of a 76 year-old female who consulted her general ophthalmologist for the first time in November 2017 complaining about painless, bilateral, rapidly progressive visual

loss. She was referred to our regional hospital for complementary investigations. We received the patient in March 2018. A thorough clinical examination included static automated perimetry, VEP recording and optical coherence tomography (OCT) of the macula and the optic nerve.

Results: The medical history revealed a right hip joint replacement in 2009 with clinical right leg metallosis features leading to ablation surgery of her right hip prosthesis in 2015. Right visual acuity (VA) was 0.6 logMAR and left VA was 0.3 logMAR. IOP was normal in both eyes (10 mm Hg). The anterior segments were normal except for discrete bilateral cortico-nuclear cataracts. Fundus examination revealed a few bilateral serous drusen and a normal appearance of optic discs and vessels. On static perimetry, bilateral central scotomas were found. OCT RNFL was normal in both eyes. VEPs revealed bilateral axonal dysfunction: no P100 response could be identified. Laboratory testing for blood levels of chrome and cobalt are in progress to confirm our suspicion of bilateral toxic neuropathy.

Conclusions: Altered VEP responses confirmed the diagnosis of toxic optic neuropathy in this patient with bilateral visual field impairment and normal findings on both OCT and angiography. Cr/Co systemic toxicity is known to cause hypothyroidism, dilated cardiomyopathy, pericardial effusion, dyspnoea, hearing loss, tinnitus, cognitive trouble and peripheral sensori-motor neuropathy. Several cases of toxic Cr/Co induced bilateral optic neuropathy with central and caeco-central scotoma or homonymous quadrantanopsia have been reported. A partial recovery of symptoms after reducing blood levels of the causal agents has been described. The definitive treatment remains surgical prosthesis ablation, but some chelation studies have shown promising results with sodium-calcium edetate, acetylcysteine or dimercaptosuccinic acid. Recent studies suggest that the major toxicological risk comes from the insertion of a Cr/Co component concomitant with residual ceramic debris.

3.15 VEP follow-up of a mitochondrial optic neuropathy

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Purpose: In early stages of optic neuropathy, visual acuity, fundus examination and visual field testing may remain unremarkable. Color vision changes and VEP abnormalities may be early signs, especially in toxic optic neuropathy. The purpose of this clinical case presentation is to report the value of VEP in diagnosis and follow-up in a case of paucisymptomatic optic neuropathy.

Methods: A 25 year-old female patient was referred for bilateral optic neuropathy. An initial complete assessment of visual function was performed, including best corrected visual acuity, static automated perimetry, and pattern VEP. Cranial and medullary MRI were normal. There was no evidence for autoimmune disease or inflammation. Serologies for human immunodeficiency virus, syphilis and Lyme disease were negative.

Results: On presentation, the patient complained of diffuse visual discomfort. Visual acuity was 25/20 in both eyes, the anterior segments were normal, and optic nerve head pallor was observed in both eyes. The OCT RNFL displayed axonal loss. Visual fields were normal and the visual evoked potential revealed axonal dysfunction. VEP the responses to both 60' and to 15' checks were normal. However, no P100 wave could be identified in response to 7' checks. A mitochondrial optic neuropathy was suspected. There was no history and no clinical evidence of alcohol abuse. Genetic testing was performed and the blood levels of common mitochondrial micronutrients (Vitamin B1, B3, B6, and carnitine) were determined. The tests revealed carnitine deficiency and PP vitamin deficiency. Visual symptoms and the responses to 7' checks progressively improved after 6 months and 12 months of supplementation.

Conclusions: Improvement of visual function after supplementation with mitochondrial micronutrients can be monitored with VEPs.

3.16 Visually evoked responses to pattern stimulation and its importance in anisometropic amblyopia

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Purpose: Ambylopia is primarily a central phenomenon caused by unequal competitive inputs from the two eyes into primary visual cortex area 17 and structural and functional abnormalities in the lateral geniculate nucleus. Ambylopia is a monocular disease and is not a static condition. It has a strong dynamic component and severity can be modified by the type of stimulation provided to the sound eye. The mainstay of treatment is occlusion of the normal, sound eye. Recent studies have revealed that binocular dysfunction plays an important role in amblyopia. The responsibility of the ophthalmologist is to suggest occlusion and follow treatment intensively. Anisometropic ambylopia may have pathophysiology caused by impairments in binocular function rather than anatomic differences in visual cortex, which explains why the patients respond simply to spectacles alone. The parvocellular pathway of the lateral geniculate nucleus is more affected. A pattern stimulus consisting of alternating white and black checks is commonly used in the clinical VEP because it generates the most vigorous and consistent cortical response. There are only a limited number of reports about pattern stimulation VEP in anisometropic ambylopia. We compared VEP responses of the ambylopic eye with VEP responses of the sound eye in ambylopic children.

Methods: In the present study, amplitude and latency of the P100 component to pattern-reversal stimulus with large check size (100 minutes of arc) were measured in 10 emmetropic normal children as controls. VEP amplitude and latency parameters were compared with VEP parameters in ambylopic children. Ambylopic children were classified as Group 1: anisometropic amblyopia, n=15 children; and Group 2: combined mechanism ambylopia (anisometropia with strabismus), n=6 children. All children underwent complete ophthalmological and orthoptic examination and pattern reversal VEP to large checks with best correction spectacles. After the complete examination, all children underwent occlusion treatment. Statistical analysis was done using the Wilcoxon matched-pairs signed-rank test.

Results: Normal group: Age [mean (standard deviation)]: 6.8(2.97), range 4 to 12 years. Amblyopic Group 1 (anisometropic amblyopia): Age 7.46(1.63), range 6 to10 years. Amblyopic Group 2 (combined mechanism amblyopia): Mean age of 7.66(2.25) with a range of 6 to10 years. Mean amplitude and latency in the normal group were as follows: P100 in RE 14.65(4.3) µV; 101.95(5.79) ms; in LE 14.72(3.66) µV; 101.7(6.35) ms, respectively. For amblyopic Group 1, analysis of interocular P100 amplitudes showed a statistically significant difference (p=0.04) with high amplitude score in the sound eye when compared with the ambylopic eye. However no statistically significant differences between sound and amblyopic eyes were found in the following parameters: Group1 P100 latency (P=0.62), Group 2 P100 amplitude (p=0.07), Group 2 P100 latency (p=0.45)

Conclusions: In the present study, pattern VEP was used because ambylopic changes are easily demonstrated with this response. It was expected that VEP responses of ambylopic eyes would have lower amplitude and longer latencies than the sound eye of ambylopic children. In the present study, only P100 amplitudes of Group 1 showed a statistically significant difference between eyes. The remaining response parameters were not significantly different in either group. Interocular P100 latencies of the amblyopic eyes in Group 1, the anisometropic ambylopia group, were similar to those of the sound eye, suggesting that the neural insult may be less severe. These findings suggest that the sound eye in ambylopic patients is not functionally normal. Special attention should be paid to ambylopia treatment, as occlusion can have a harmful effect on the sound eye. New treatment approaches should be designed in the future to treat binocular dysfunction.

3.17 VEP-misrouting in albinism: evaluation of currently used methods

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Purpose: Foveal hypoplasia and chiasmal misrouting are two important diagnostic signs of albinism. With the increasing use of optical coherence tomography (OCT), more mildly affected albinism patients are detected with higher visual acuity (VA). Misrouting is established by VEP measurements. Currently used asymmetry assessment techniques are the Pearson's correlate (pc), calculated from the first 200 milliseconds (ms), and the chiasm coefficient (cc) for which a window of 60-300 ms is used. Flash VEP is used in young patients and pattern VEP in adults. There is no consensus as to what ages flash VEPs should be used alone or in combination with pattern onset VEPs (Apkarian *Ophthalmic Paediatr Genet* 1992;13:77-88; Kriss et al*. Ophthalmic Genet* 1990;11:185-92; Neveu et al. *Eur J Neurosci* 2003;18:1939-49). The purpose of this study was to evaluate current misrouting assessment techniques for different ages and visual acuities.

Methods: We retrospectively analyzed VEP recordings of 71 genetically confirmed albinism patients. VEPs consisted of pattern onset (check sizes 60' and 15', 200/400 ms), acuity sweep (pattern onset with check sizes 60', 30', 15' and 7.5', 40/260 ms shown one after the other), flash colordome (3 cd·s/m^2, 1.09 Hz), and hand-held flash colorburst (3 cd·s/m2, 2.5 Hz), depending on the cooperation of the patient. Three age groups were evaluated: < 3 years old (yo), 3-6 yo, and > 6 yo. We compared the cc in windows of 60 to 300 ms and 60 to 200 ms for all stimuli. In the 60-200 ms window, we compared the pc and cc. Based on previous results, we considered a cc of < -0.2 as proof of misrouting (Jansonius et al. *J Neuroophthalmol* 2001;21:26-9; Pott et al. *Doc Ophthalmol* 2003:137-43). We also investigated if sensitivity of misrouting detection differed based on visual acuity: patients with no to mild impairment (logMAR VA ≤ 0.3), mild to moderate impairment (0.3 < logMAR VA < 0.7), and moderate to severe visual impairment (logMAR VA ≥ 0.7).

Results: Highest sensitivity was found: a. for patients ≤ 3 yo with Colorburst (96%, 23/24); b. for patients 3-6 yo with colorburst (91%, 30/33) and with acuity VEP check sizes 15'and 7.5' (100%; 4/4); c. for patients ≥ 6 yo with acuity VEP check sizes 60' and 30' (94%, 16/17). In all groups, the cc was significantly more negative than the pc. Sensitivity was higher for a 60-200 ms window than for a 60-300 ms window. With the acuity sweep (check sizes 60' and 30'), sensitivity was equally high for all visual acuities (83-100%).

Conclusions: The cc was significantly more negative than the pc. A smaller window (60-200 ms) resulted in a higher sensitivity. Sensitivity of flash colorburst is only high in patients under six yo or patients with very poor VA (≥ 0.7 logMAR). In patients older than six, especially in patients with better VA, acuity sweep check sizes 60' and 30' seem to be more effective than pattern onset and flash for the detection of misrouting. The use of acuity sweep needs further investigation in younger patients. These conclusions will be tested in a control group for specificity.

3.18 Diagnostic performance of photopic ERGs in a population who visits optometrists and ophthalmologists

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Purpose: To assess the utility of photopic ERGs as an objective aid to detect any retinal disease in a population who visits optometrists and ophthalmologists.

Methods: In three ophthalmology and two optometry centers in the USA, all patients coming for a normally-scheduled visit were asked to participate. Subjects were tested with dilated or natural pupils based on what was required for their normal examination. Subjects with dilated eyes had one randomly-selected eye tested, while natural pupil subjects had both eyes tested. Dilated subjects were tested with eight constant-luminance (candela-based) protocols and two ISCEV-equivalent Troland-based protocols that compensate for pupil size. Natural-pupil subjects were tested with 11 Troland-based protocols. Pediatric subjects less than eight years of age used a shorter test set; subjects aged 8–12 years old were given a choice as to the testing length. Subjects were classified as normal if the following criteria were met for both eyes: best corrected visual acuity (BCVA) of 20/25 (0.1 logMAR) or better, optic nerve cupping < 50 %, no glaucoma or retinal diseases, no prior intraocular surgery (excepting non-complicated cataract or refractive

surgery performed more than one year before), intra-ocular pressure ≤ 20 mm Hg, no diabetes, and no diabetic retinopathy as determined by the ophthalmologist or optometrist. Eyes were classified as diseased if the physician detected glaucoma, diabetic retinopathy, or other retinal diseases in either eye. Clinicaltrials.gov identification NCT03065881.

Results: To date, 594 subjects have been tested, 253 of whom were classified as normal and 158 of whom were classified as diseased. Self-reported race was 49% Caucasian and 34% African American in the normal group and 28% Caucasian and 64% African American in the diseased group. About 13/18% self-reported as Hispanic in the normal / diseased groups. The gender distribution was 65/61 % female in the normal/diseased groups. At the time of testing, 38/61% of subjects had been artificially dilated in the normal/diseased groups. The most common diseases were glaucoma (47%), diabetic retinopathy (30%), optic atrophy (17%), hypertensive retinopathy (10%), age-related macular degeneration (AMD, 6%), and retinal vein occlusion (RVO, 4%). Reference ranges were determined using the normal subjects. Subject's ERGs were considered abnormal if either the amplitude was smaller than a given percentile in the reference data or if the peak times were longer than the same percentile. Brief flash flicker tests best separated diseased from healthy, with an area under the receiver operating curve (ROC) of 85% for the 16 td s flicker ERG. One point on that ROC curve had a sensitivity of 81% and a specificity of 83%.

Conclusions: We considered the utility of a simple photopic ERG as an initial aid to the doctor in assessing the presence of retinal disease (e.g., in a general office visit). As shown here, a 16 td s flicker ERG may have sufficient performance to meet this need. We are continuing to test subjects to increase the confidence in these measurements and plan to determine if combinations of ERG tests and/or visual acuity can improve diagnostic performance. Limitations of the study include imperfect racial matching between diseased and healthy groups, and our disease distribution may not be representative of the disease distribution everywhere.

Funding: LKC Technologies, Inc.

3.19 Pattern-reversal and motion-onset VEPs vs. contrast sensitivity

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Purpose: To evaluate whether contrast sensitivity is independent of high contrast pattern-reversal VEPs (PVEPs) and low contrast motion-onset VEPs (M-VEPs) in the evaluation of the visual system.

Methods: In a group of 263 subjects (119 males and 144 females, age 8-82 years) with visual disturbances of various aetiologies, we measured contrast sensitivity using the CSV-1000 table (for 3, 6, 12 and 18 c/deg: CS3, CS6, CS12, CS18). At the same time we recorded PVEPs to high contrast (96%) reversing checkerboard of 10', 20' and 40' checks, and M-VEPs to onset of radial motion of low contract (10%) concentric circles in full-field, central 8°, and periphery outside of the central 20°. A correlation analysis was conducted on separate eyes for peak times (P100 and N2), interpeak amplitudes, logarithmically transformed contrast sensitivity, and visual acuity. Results were corrected for multiple comparisons (all p-values below are corrected). To evaluate contribution of the contrast sensitivity to the variability of the selected significant parameters, we used multiple regression analysis.

Results: The correlation analysis highlighted a statistically significant relationship of PVEP P100 peak time to contrast sensitivity. The highest Spearman rho (-0.35; $p<<0.001$) was found between CS18 and the P100 peak time of PVEP to 20' checks. A similar significant negative relationship was also present for other PVEPs in CS6, CS12, and CS18. The only two significant correlations for PVEP amplitudes were for PVEP R20' and P-VEP R0' to CS18 (rho > 0.16, $p < 0.03$). Centrally evoked M-VEPs showed a significant relationship of the N2 peak time to contrast sensitivity (in all spatial frequencies rho was from -0.16 to -0.19, $p<0.015$). The peripheral M-VEPs were related only to CS12 and CS18 (rho = -0.16 and -0.18, $p<0.033$). There was no significant correlation of any M-VEP amplitude to the contrast sensitivity. Regression analysis showed that the CS3 and CS18 explained 18% of the peak time variability of the PVEP 20'. For centrally-evoked as

well as for peripherally-evoked M-VEPs, regression analysis showed that contrast sensitivity cannot explain peak time variability above the visual acuity.

Conclusions: The relationship between PVEPs and contrast sensitivity was statistically significant and more pronounced for peak time than for amplitude. This relationship explains only a limited portion of peak time variability. The absence of significant relationships between contrast sensitivity and M-VEPs amplitudes suggested that these measures are independent. Future research should evaluate sensitivity and specificity of these partially independent measures in different clinical conditions.

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3.20 LED flash stimulation compared to Grass strobe photic stimulation

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Purpose: The Grass strobe photic stimulator is a gold standard for neurophysiological and paediatric electrophysiological tests. This equipment is no longer produced. The aim of this study was to appraise hand-held LED stimulators as substitutes for the Grass strobe in paediatric retinal testing.

Methods: We first carried out a photometric study of flashes produced by a Grass strobe and two different hand-held LED stimulators; one design used one LED in a purpose built unit; the other used four LED engines positioned in a Grass bulb holder. We measured the average luminance of each stimulator for the range of settings directly and reflected in a Ganzfeld using an IL1700 photometer. A graphical representation of the distribution of direct light at different angles from the centre point of each stimulator was plotted. We chose averaged luminance values of flashes for each LED stimulator that matched Grass flashes most closely.

Results: Using the reflected luminance values, the first LED stimulator (LED-1) settings matched to the Grass stimulator for settings gr1, gr2 and gr4. The gr4 setting (7.8 cd/s/m2) was closely matched to the maximum LED-1 setting used, at 4 ms duration, with a luminance of 8.2 cd s/m2. This LED stimulator did not match gr8 or gr16 settings within the 4 ms duration used. The second LED stimulator (LED-2) had four LEDs and matched gr1, gr2, gr4 and gr8 Grass stimulator settings. The maximum LED luminance value of 30.21cd.s/m^2 achieved with 5 ms duration approached 37 cd s/m^2, the Grass stimulator maximum gr16. The light distributions of the LED stimulators were more uniformly distributed than the Grass strobe, but Grass strobe luminance decreased more gradually away from the centre compared to the single LED stimulator, which had a narrower field of maximal luminance.

Skin ERGs evoked by the three stimulators will be discussed.

Conclusions: The 1-LED device matched Grass strobe gr4, which is suitable for flash VEP neurophysiological standards, but not paediatric visual electrophysiology. The 4-LED device matched Grass strobe gr8 and approached gr16 potentially making it a suitable substitute for the Grass stimulator.

3.22 Modifying the manufacturer's recommended dark adaptometry protocol for use in a clinical setting

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Purpose: Dark adaptometry is an effective complementary tool to electrodiagnostic tests, monitoring the patient's rate of adaptation to scotopic conditions by measuring the threshold of dim light perception over time, following a period

of bright light exposure which acts to bleach the photoreceptors. This can inform the clinician regarding the presence and severity of night blindness conditions and pick up delays in dark-adaptation, diagnose rare rhodopsin disorders such as Fundus albipunctatus/Oguchi disease, or post photo-receptor issues that cannot be detected by the ERG. The Roland Dark Adaptometer (DA) has a number of features that improve greatly upon the manual Goldmann-Weekers DA system previously used (e.g. displays two distinct curves for rod and cone dark-adaptation, making visualisation of the rod-cone break (a measure of rate of adaptation) much easier; digital recording of results; non-central fixation for more sensitive measurement of rods at their densest area of distribution; and programmable LEDs. The manufacturer-recommended test parameters were more suited to research purposes than for a routine clinical setting, including a painfully bright bleaching light of 7000 cd/m2 that photophobic patients would be unlikely to tolerate. Roland also recommends performing the test twice, each eye separately, which could take over an hour. The presentation light is also presented quite rapidly, requiring a great deal of concentration on behalf of the patient and could result in unreliable responses, particularly for paediatric patients. These issues have been addressed in this study.

Methods: Various parameters (bleaching intensity, bleaching duration, and pupil dilation) were varied using one volunteer, in order to modify the test protocol to something that could be tolerated by patients, whilst still acquiring clinically useful results. The proposed changes were subsequently checked with five other volunteers to ensure that bleaching was sufficient to produce a clear rod-cone break in all cases.

Results: We have developed parameters to improve use of this device as a clinical tool: 1) 1000cd/m2 bleaching for 10 minutes with dilated pupils; 2) improved stimulus timing, including a paediatric protocol with longer allowable reaction times; 3) an abbreviated protocol: entire test requiring ~30 minutes inclusive of a single binocular bleaching phase. The better eye (if applicable) is patched during dark-adaptation to obtain full rod-cone break and final threshold results from the less sensitive eye. Final thresholds are measured for the other eye by changing the patch whilst still in the dark. We also found that the initial volunteer had the quickest rate of dark adaption compared with the rest of the volunteer cohort. As the rod-cone break was observable, this demonstrated that bleaching was sufficient. If bleaching was insufficient, the rod-cone break may occur, effectively, before commencement of dark adaptation.

Conclusions: A revision to the manufacturer's protocol has been developed for the clinical setting. This should be tested in other centres with the aim of generating an agreed protocol and to creating a shared database of reference ranges.

3.23 Evaluation of a long-term toxicity screening programme using mfERG in hydroxychloroquine patients

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Purpose: The potential of retinal toxicity due to hydroxychloroquine is well recognised. However, worldwide management of ocular safety in patients taking the drug is highly dependent on regional standards of best practice. This department has instituted a rigorous screening programme based on current American Academy of Ophthalmology Guidelines using the mfERG. The purpose of this study is to evaluate the benefit of the programme through measurable changes in management of patients over time.

Methods: Patients referred from major tertiary institutions and private specialists were tested using the mfERG. Results along with demographic data, drug dosing regimen, primary indication for drug use, known risk factors, and clinical information were stored in a database. Patient visits were grouped and analysed according to three triennial periods commencing in 2009 to investigate trends in drug management and prevalence of toxicity.

Results: Demographics: The number of patients tested in the three periods starting in 2009, 2012 and 2015 respectively were 494 (F=83%, M=17%), 648 (F=85%, M=15%) and 1073 (F=86%, M=14%). Age (years): 55.7±13.97 (range 11-8), 54.1±15.04 (range 14-88), and 55.1±14.48 (range 8-90). Indications for drug use in the first group were documented as rheumatoid arthritis, systemic lupus erythematosus, Sjogren's syndrome, mixed connective tissue disease or other, but in the last group the list had grown to 87 distinct categories, with common autoimmune diseases such as diabetes, multiple sclerosis, psoriatic arthritis,

Crohn's, Addison's, Graves', and coeliac diseases included. Drug dosing: The minimum ages of commencing treatment were 11, 8 and 2 years respectively. The daily doses for the three groups respectively were 5.70±3.86, 4.89±2.40, and 3.51±1.77 mg/kg. Corresponding durations of treatment were 7.99±7.56, 8.38±7.87, and 8.86±7.71 years. The percentage of patients taking higher than standing current recommended safe dose limits were 43%, 33%, and 20%. Toxicity: The incidence of toxicity measured by mfERG in the three groups was 35%, 20%, and 28%, respectively. The last group included 352 (33%) new patients who had not previously been screened despite being on the drug for over 7 years.

Conclusions: There has been a significant drop in the percentage of patients taking higher than recommended safe dosing limits and a corresponding decrease in daily dose. The authors believe that this is a direct result of both improved documentation of safe practice guidelines and reinforced education of patients and their prescribing practitioners through the screening programme. The age of starting long-term therapy is now as low as two years, implying much longer periods of treatment in the future. Moreover, the range of primary indications is widening. It is therefore more important than ever to maintain safe use of this important drug through evidence based practice. This study demonstrates the benefit of a well-regulated screening programme to maintain safe dosing in patients.

3.24 Traps and tips to perform the multifocal electroretinogram (mfERG)

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Purpose: To report common traps in carrying out the mfERG and to propose some keys to avoid them.

Methods: Based on clinical cases, we have collected various situations producing difficulties in performing the mfERG that can lead to errors in the interpretation of its results. We report how we have proceeded to resolve them.

Results: The choice of the active electrode, a bubble under the corneal electrode, and difficulty in positioning glasses properly represent the main technical problems. Refractive error, especially including astigmatism and high refractive error, constitute the optical problem. Ptosis, corneal pathology, lens opacities, history of refractive surgery, and eccentric fixation reflect anatomical causes. We have regularly noticed the instability of fixation and patient contortion. In very severe impairment, we observed some false responses due to the recording of noise. At each stage of the exam, we propose how to identify the different traps that can lead to misinterpretation and how to manage them.

Conclusions: The mfERG is a fundamental procedure of visual electrophysiologic testing. It is essential to perform it rigorously: the quality of the results is decisive for their validity and is critical for accurate medical diagnosis. Knowing the tips to avoid the most common traps is particularly useful.

3.25 Effect of defocus induced by multifocal contact lens of dominant and non-dominant design on the amplitude and implicit time of the mfERG

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Purpose: The objective of this work was to analyze the influence of different levels of defocus induced by different designs of multifocal contact lenses (MFCL) on the bioelectric activity of the retina measured with the mfERG.

Methods: The mfERG of 10 eyes of 10 young healthy emmetropic subjects with visual acuity of logMAR 0.00 or better in both eyes, normal color vision, and good ocular health were obtained with four different MFCL and compared to the naked eye. The mfERG was measured with the RETI-port/scan 21 gamma plus2 (Roland Consult, Germany) using DTL fiber electrodes and followed the ISCEV standard. The pupil was fully dilated with two drops of 1% Davinefrina and a stimulus pattern of 103 hexagons, scaled with eccentricity, was presented on a 19inch RGB monitor. The amplitude (nV) and implicit time (ms) of the wave components (N1, P1) of the first Kernel response were analyzed in six concentric rings (maximum eccentricity ~ 33 deg) under five different conditions: naked eye, with a MFCL of center-distance design with Add=1.50 (MFD15), MFCL of center-distance design with Add=2.50 (MFD25), MFCL with center-near design with Add=1.50 (MFN15), and MFCL with center-near design with Add= 2.50 (MFN25).

Results: When compared with naked eye, the mean N1 amplitude significantly decreased with all MFCL designs in Ring 1, Ring 3 and Ring 6 ($p<0.05$). The mean P1 amplitude also showed a significant reduction in Ring 1 for MFCL of center-near design ($p<0.05$, in both N designs) and showed a significant reduction in all MFCL designs for Ring 3, Ring 4, Ring 5 and Ring 6 ($p<0.05$, in all rings and conditions). For implicit time, there was an increase in both N1 and P1 wave components, being significant in the paracentral and more eccentric rings (Ring 2 to Ring 6, $p<0.05$). In the central region (Ring 1), the increase in implicit time was significant with the center-near design (N15 and N25, $p<0.05$). The analysis by quadrants showed a significant increase in implicit time for the inferior nasal and temporal region for both N1 and P1 wave components, while in the superior

nasal and temporal region, there was a significant decrease in both N1 and P1 amplitude ($p<0.05$).

Conclusions: From these preliminary evaluations, we observed a significant reduction in amplitude and delay in time of the wave components of the retinal response obtained by multifocal ERG when different levels of defocus are induced by multifocal contact lens with different designs.

3.26 The influence of different contact lens material on the mfERG

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Purpose: Electrophysiologists have been using contact lens (CLs) to develop new electrodes to record the retinal electrical signal. In fact, CLs are often more comfortable, though they may create a weaker signal with less distortion in the electrical transmission compared with other corneal electrodes. The main goal of this study was to evaluate the influence of three different CLs materials: one from a rigid scleral contact lens (ScCLs), one hydrogel and one silicone hydrogel soft contact lens (SCLs).

Methods: The electrophysiological response of the retina from 18 right eyes of young healthy volunteers, with refractive error near emmetropia, was evaluated with SCLs (mean age 26.72±7.11 years; n=11, seven females) and ScCLs (32.6±9.7 years; n=7, three females). Baseline measurements were taken before CL insertion. The pupil was fully dilated with two drops of 1% phenylephrine and the left eye was occluded. The mfERG response was recorded with the RETIport/scan 21 (Roland Consult, Germany) using a DTL electrode and a stimulus pattern of 103 hexagons scaled with eccentricity on a 19 inch RGB monitor. The amplitude (nV) and implicit time (ms) of the wave components (N1, P1) of the first Kernel response were analyzed in six concentric rings (maximum radial eccentricity ~ 33º). Two SCLs (Omafilcon A and Comfilcon A) and one rigid ScCL (Hexafocon A, Ø=16.40mm, sagittal depth=4673µm; Procornea Med+, Eerbeek, Holland) with spherical power of 0.00D were used.

Results: The results showed that Omafilcon A had significant reduced values in the implicit time of N1 peak of the total mfERG response and at Rings 1, 5, and 6, compared with no contact lens and Comfilcon A ($p<0.016$, Wilcoxon Test). The same was observed for the implicit time of the P1 peak compared to Comfilcon A values for the total mfERG response and at Ring 2 and Rings 4 to 6 ($p<0.042$, Wilcoxon test). With respect to the amplitude of the mfERG response, we observed that once again, Omafilcon A produced a higher N1 and P1 peak amplitude in the total response and at peripheral rings (Ring 4 to 6) compared to baseline values and Comfilcon A, respectively ($p<0.033$, Wilcoxon test). Regarding the ScCL material, the overall mfERG peak times and amplitudes of N1 and P1 wave peaks and of all rings did not significantly change with ScCL use ($p>0.070$, Wilcoxon test). However, the peak time of N1 was longer with the ScCLs (26.75±5.36 ms) than with no lens (23.01±4.64 ms) in Ring 1, but with a non-statistically significant trend ($p=0.404$, Wilcoxon test).

Conclusions: In general, Omafilcon A material apparently reduced the implicit time lag and increased the amplitude of the mfERG response of the retina, especially at more peripheral areas, whereas the ScCL material did not affect the mfERG response. These results have implications for future applications of mfERG strategies to evaluate retinal function in subjects using SCLs for ametropia correction or myopia progression control, as well as in patients with corneal abnormalities and poor vision.

Wednesday 20th June 2018, 15:15–17:00

Session 4: Paper Session — Paediatrics

4.01 Paediatric pattern-reversal VEP reference intervals

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Purpose: Adequate reference data are required to determine normality of VEP parameters. The gold standard for determining reference intervals requires large (>120) numbers of healthy subjects, selected a priori, which is costly and time-consuming. Centres may choose to use reference values from scientific or commercial literature or to base clinical decisions on an inadequate reference dataset. An alternative option is the indirect or a posteriori method, which uses mathematical procedures in combination with exclusion criteria on retrospective patient data. Here, we combined healthy children's reference data acquired at two UK paediatric visual electrophysiology centres and compared the reference limits from these data with reference limits derived from patient data from one centre using the indirect method.

Methods: Binocular pattern reversal VEP parameters from three populations were used: 1) 180 healthy infants and children aged 5 weeks–16 years tested at the Royal Hospital for Children, Glasgow (RHCG); 2) 188 healthy infants (N=166, aged <52 weeks) and children (N=22, aged 5–16 years) tested at Great Ormond Street Hospital, London (GOSH) and; 3) 889 patients, aged 3 months–19 years, tested at GOSH between 2014 and 2017. VEPs were recorded from Oz referred to Fz in response to high contrast checkerboards reversing once (RCHG and GOSH <8 weeks) or three times (GOSH >8 weeks) per second, presented in a 30° field following the ISCEV VEP standard. Peak times and amplitudes of P100 to large (50' GOSH, 60' RHCG) and to small (12.5' GOSH, 12' RHCG) check widths were analysed. Standard verification processes were used to test the extent to which data from the two centres could be combined. After appropriate outlier removal and data transformation, reference limits with associated 90% confidence intervals were defined.

Results: Data were comparable between the two centres (<10% of data points falling outside reference intervals defined by larger dataset), except for slightly smaller 60' check P100 amplitudes for RHCG infants. All data for the two centres were combined since this difference was small and affected only amplitude which is much more variable and less reliable for clinical decisions than peak time. No gender effect was evident. There was a rapid drop in PVEP peak time during infancy which stabilised by the end of the first year for 60': thereafter, reference limits were 90 ms (90% CI 88–91 ms) to 112 ms (90% CI 109–121 ms). For 12' check widths, PVEP peak time stabilised by 18 months; thereafter reference limits were 95 ms (90% CI 93–97 ms) to 140 ms (90% CI 136–153 ms). 60' PVEP amplitude peaked around 6 years while 12' amplitudes peaked around 3 years: some infants <1 year had no 12' VEP. Patient data clustered largely within reference ranges from healthy infants and children, with longer peak time outliers and distribution skewed to longer peak times.

Conclusions: These data suggest that reference data collected using ISCEV Standard protocols are likely to be amenable to combining into larger datasets, with resultant smaller errors on reference limits and increased diagnostic power. This is seen even with the current datasets, where some deviations in protocol within the tolerances of the ISCEV VEP Standard (3 vs 1 reversals per s for infants >8 weeks; dim vs normal room lighting; 60–80 vs 50 cd /m2 mean luminance; 50 vs 60' check side width) nonetheless produced comparable reference datasets. Patient data lay predominantly within reference ranges from healthy infants and children, suggesting another means of accessing large numbers to define robust reference intervals.

4.02 Visual electrophysiology testing in infants with congenital vertical nystagmus

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Purpose: In the present study, we describe the visual electrophysiology findings and underlying aetiologies of congenital vertical nystagmus (CVN) with special attention to inherited retinal diseases. The main goal was to establish a strategy of exams in the setting of CVN.

Methods: Our retrospective cohort included all paediatric patients with diagnosis of CVN. All patients underwent complete ophthalmic examination with nystagmus video, visual electrophysiology testing (VEP + ffERG), neuropediatric examination and brain MRI.

Results: We recruited 45 patients with CVN from 2006 to 2017. On the basis of nystagmus video analysis, 35% of infants had an up-beat nystagmus, 30% had a down-beat nystagmus, 25% had a pendular vertical nystagmus, and 10% had a vertico-torsional nystagmus. Overall, 37% of patients had abnormal visual electrophysiology findings (14/45 had abnormal VEP and ERG; 3/45 had abnormal VEP only) and have been diagnosed with anterior visual pathway disease. The main ophthalmic aetiologies of CVN were: stationary photoreceptor dysfunction syndromes (achromatopsia, blue cone monochromacy, congenital stationary night blindness), and early retinal degenerations (non-syndromic Leber amaurosis, Joubert syndrome, neuronal ceroid lipofuscinosis). Two cases of optic nerve gliomas were discovered. 38% of CVN were "neurological" in origin (inborn encephalopathies). 17% were diagnosed as idiopathic. Interestingly, there were no abnormalities of VEP/ERG in the group of down-beat congenital nystagmus.

Conclusions: Visual electrophysiology testing is highly productive in the setting of CVN. Anterior visual pathway diseases were as frequent as neurological conditions in patients with CVN. In our cohort, stationary retinal dysfunctions and early retinal degenerations were prominent ophthalmic aetiologies of CVN. We suggest that a thorough ophthalmic examination, including visual electrophysiology testing (VEP + ffERG), combined with neuropediatric examination and a brain MRI should be obtained in all infants with CVN.

4.03 Comparison of flash visual evoked response between clinically stable preterm infants and term healthy infants

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Purpose: This study aimed to investigate the visual pathway conducted cortical response of Nepalese clinically stable 6 month old preterm and full-term infants using Flash VEP and to determine the association of VEP parameters with birth weight (BW) and gestation age (GA).

Methods: Twenty-five preterm and twenty-five full term infants underwent Flash VEP examination, under normal sleeping conditions, according to the ISCEV guidelines. Cortical response in terms of wave latency and wave amplitude were recorded. VEP parameters were compared between preterm and full-term infants using the independent sample t-test. Correlations of latency and amplitude with GA and BW were determined using linear regression analysis and ANOVA.

Results: At the age of 6 months, the preterm group had a greater amount of myopic refractive error than the full-term group. There was a significant delay in the P2 wave latency for the preterm group at both low and high frequencies for both eyes ($p<0.05$ for RE, $p<0.05$ for LE). N2P2 wave amplitude showed significantly reduced values in the preterm group compared with the full-term group at both the frequencies ($p=0.010$ for RE; $p=0.004$ for LE). There was a positive correlation between N2P2 wave amplitude and GA ($r^2=0.217$, $p<0.01$), and a negative relationship of P2 wave latency with BW ($\beta=0.380$, $p<0 .05$) and GA ($\beta=-0.625$, $p<0.05$).

Conclusions: Preterm infants who were considered clinically stable showed an increase in VEP latency and a decrease in amplitude compared to full-term infants at 6 months of age.

4.04 Do pattern VEP, PERG and focal ERG allow an early functional diagnosis in insulin dependent diabetic (IDDM) children without diabetic retinopathy?

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Purpose: To evaluate the transient pattern VEP (t-VEP), steady state pattern VEP (s-VEP), transient PERG (t-PERG), steady state PERG (s-PERG) and focal ERG (FERG) in eyes of IDDM children without retinopathy.

Methods: In 40 eyes of 20 IDDM children and in 40 eyes of 20 age and sex matched healthy controls, monocular VEPs and PERGs were recorded according to the ISCEV standards. FERG was recorded using a TV monitor as stimulator. Best corrected visual acuity (BCVA) was 10/10 in all subjects in both groups. For the VEP silver/silver chloride skin electrodes were used. The recording electrode was placed at Oz, the reference electrode at Fpz, and the ground electrode on the nasion. For the t-VEP, peak to peak amplitude and implicit time of N75, P100, and N125 were evaluated; for the s-VEP, amplitude of the second harmonic and phase were calculated. For the PERG, silver/silver chloride skin electrodes were used. The recording electrode was placed on the inferior right lid, the reference electrode on the inferior left lid, and the ground electrode on the nasion. For the t-PERG, the peak to peak amplitude of N35, P50, and N75 was evaluated; for the s-VEP, the amplitude of second harmonic and the phase delay were examined. For the FERG, after instillation of anaesthetic drops, DTL electrodes, placed in both inferior fornices, were used as active electrodes; silver/silver chloride electrodes were used both as reference electrodes, positioned symmetrically on both temples, and as ground electrode attached to the nasion.

Results: Compared to controls, in diabetic patients we observed: for t-VEP, a significant reduction of P100 amplitude of ($p<0.05$) and a significant increase of P100 implicit time ($p<0.01$); for s-VEP, a significant decrease of the amplitude of second harmonic ($p<0.001$); for t-PERG, a significant reduction of P50 amplitude ($p<0.001$); for s-PERG, a significant reduction of the amplitude of second harmonic ($p<0.05$); and for FERG, a significant decrease of the amplitude of the fundamental harmonic ($p< 0.001$).

Conclusions: Pattern VEP, PERG, and FERG are objective and non-invasive means of evaluating the function of the visual pathway. In IDDM patients, the most reliable electrophysiological parameters for an early diagnosis are: t-VEP P100 amplitude and implicit time, s-VEP second harmonic amplitude, t-PERG P50 amplitude, s-PERG second harmonic amplitude, and FERG 1F component amplitude.

4.05 The effect of grating stimulus orientation on monocular pattern-onset VEP and psychophysical grating acuity in young children with newly-diagnosed refractive amblyopia

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Purpose: Refractive amblyopia often occurs in young children with moderate to high degrees of astigmatism due to meridional retinal image blur and reduced cortical input in those orientations. Meridional anisotropies (horizontal different from vertical) have been found for grating acuity (GA) in young astigmatic children with visual acuity (VA) 6/9 or poorer (Dobson et al., *Ophthalmology*. 2009;116(5):1002-8), but it is unclear whether orientation-specific attenuations in pattern-onset VEP (POVEP) will occur along the principal astigmatic meridians. The purpose of this study was to assess whether there are meridional anisotropies along the astigmatic meridians in young children newly diagnosed with amblyopia who have not yet undergone spectacle treatment. It was hypothesized that lower POVEP amplitudes, longer peak latencies and poorer GA would be associated with grating stimuli presented along the more optically defocussed of the principal astigmatic meridians and in the eye with the poorer VA.

Methods: Subject inclusion criteria were young children newly-diagnosed with unilateral or bilateral refractive amblyopia without strabismus. All children underwent ocular health, VA (EDTRS), binocular vision and refraction assessment by ophthalmologists and optometrists at KK Women's and Children's Hospital. Transient POVEPs were

recorded monocularly using the Espion system (Diagnosys, Cambridge, UK) in response to 4 cpd sine-wave gratings oriented along the subjects' principal astigmatic meridians. Psychophysical GA was assessed monocularly along the same meridians using a 2-alternative-forced-choice, 2-up-1-down staircase. Stimuli were generated on a calibrated monitor using ViSaGe (Cambridge Research Systems, UK). Linear mixed model (LMM) analysis was used to investigate the effect of meridian on the dependent variables of GA and POVEP C3 amplitude and peak latency. Subject identifier was the subject variable; eye status (better, poorer, or equal VA), meridian (on- or against-axis), meridional refractive error (dioptric power in each principal astigmatic meridian), and age were entered as fixed effects.

Results: Twenty-five children [age 4.9 (range 3.3-7.1) years] with bilateral (n=19) and anisometropic (n=6) amblyopia completed the study. LogMAR VA (mean VA was 0.30 (SD 0.14) for right eyes (RE) and 0.32 (SD 0.14) for left eyes (LE). Average refractive errors (sphero-minus cylinder form) were RE -0.04/-2.37, LE +0.28/-2.57; axes ranged from 0-180, mostly following with-the-rule astigmatism. Logarithmic transformation was applied to satisfy normality assumptions of LMM. There were no significant effects of meridian on C3 amplitude or latency, but higher log-GA was associated with the against-axis meridian (p=0.002; Estimate=0.36) and less negative meridional refractive error (p=0.002; Estimate=0.07). Less negative refractive error was associated with higher log-amplitude (p=0.003; Estimate=0.10). Eyes with poorer VA were associated with lower log-amplitude (p=0.05; Estimate=-0.25). Having equal RE and LE letter VA was associated with longer log-peak latencies (p=0.008; Estimate=0.17).

Conclusions: Meridional anisotropies were observed for psychophysical GA, poorer VA consistent with the most optically defocussed meridian as predicted based on refractive errors. The POVEP amplitudes were lower in the meridian that had more negative refractive error (and was more optically defocussed), and in the eyes with more amblyopia. The differences in the POVEP and psychophysical responses warrant further investigation.

4.06 VEP monitoring of treatment for glioma of the optic pathways in young children: clinical case reports

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Purpose: Optic pathway glioma is a rare childhood brain tumor, associated with neurofibromatosis in 50% of cases.

It is histologically a benign tumor but often has severe visual complications. The current treatment is chemotherapy. Chemotherapy indications are either related to the volume of the tumor or to the ophthalmological signs. Follow-up, consisting of MRI and ophthalmological examination, is difficult because of the young age of the children.

Methods: All children examined had ophthalmic clinical examination, VEP, ocular coherence tomography (OCT) if possible, and MRI. VEPs were recorded every 4 or 6 months. Their interpretation was compared to MRI results and discussed with oncologists and neurosurgeons to adapt treatment to tumor progression.

Results: From clinical cases, we demonstrate the role of VEP monitoring in the follow-up of these tumors, particularly when MRI does not serve as a sufficient guide to therapeutic planning.

Conclusions: VEPs have a key role in the monitoring of optical pathway glioma treatment in young children.

4.07 Albinism: diagnostic criteria

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Purpose: Ophthalmic characteristics of albinism include non-progressive reduced visual acuity, nystagmus, iris transillumination, foveal hypoplasia, fundus hypopigmentation, and chiasmal misrouting. Clinical signs show considerable variability in patients, which can make the distinction from disorders with similar characteristics difficult. Idiopathic Infantile Nystagmus (IIN) is the most prevalent differential diagnosis while foveal hypoplasia, optic nerve decussation defect and anterior segment abnormalities (FHONDA) may be the most difficult. Furthermore, Caucasians may be light skinned and have mild fundus hypopigmentation in the absence of albinism. We therefore retrospectively investigated a large cohort of albinism patients with the purpose of determining diagnostic criteria.

Methods: We collected clinical, genetic, and electrophysiological data from 522 patients with albinism. We used grading schemes for fundus hypopigmentation, (0-3, with 0 being normal), iris transillumination (0-4), and foveal hypoplasia (0-4, Thomas et al. *Ophthalmology* 2011;118:1653-60). Patients were included on the basis of: 1) a confirmed molecular diagnosis of albinism or 2) hypopigmentation (skin and hair and/or fundus) accompanied by at least two of four ophthalmic characteristics of albinism, i.e. nystagmus, iris transillumination, foveal hypoplasia, chiasmal misrouting. Misrouting was established with pattern-onset VEP in patients ≥6 years old, flash VEP for patients ≤3 years old, and both pattern onset and flash VEPs in patients between 3 and 6 years old. We calculated a chiasm coefficient (cc) (Jansonius et al. *J Neuroophthalmol* 2001;21:26-9). We considered a cc of <-0.2 proof of misrouting, a cc >-0.2 and <0.0 was defined as uncertain. Mutation analysis was done in 197/522 patients or second-degree family members. Diagnosis was genetically confirmed in 153/197 patients.

Results: In 7.7% (40/521) nystagmus was absent. Iris transillumination could not be detected in 8.9% (44/492). 3.8% (19/496) had completely normal fundus pigmentation. 0.7% (3/455) had no foveal hypoplasia. In 16.1% (49/304) chiasmal misrouting could not be proven.

Conclusions: In the Caucasian population, mild hypopigmentation of skin, hair and fundus may be physiological. We therefore propose diagnostic criteria for albinism. Major criteria would be: 1) a confirmed molecular diagnosis, 2) foveal hypoplasia grade 2 or more, 3) chiasmal misrouting, 4) ocular hypopigmentation, either iris transillumination or grade 2 or more fundus hypopigmentation. Minor criteria would be 1) nystagmus, 2) hypopigmentation of skin and hair compared to siblings and parents 3) grade 1 fundus pigmentation, 4) foveal hypoplasia grade 1. We propose that three major criteria or two major criteria accompanied by two minor criteria are necessary for the diagnosis. In this manner, albinism can clinically be distinguished from IIN on the basis of misrouting and ocular hypopigmentation and from FHONDA on the basis of iris transillumination and/or fundus hypopigmentation. Of 138/522 patients for whom all clinical and electrophysiological investigations were performed, 4/138 did not meet our proposed diagnostic criteria, leading to a sensitivity of 97%.

Thursday 21st June 2018, 9:15–10:30

Session 5: Paper Session — Methods & Innovations II

5.01 Quantitative calibration of sensor strip ERG electrodes

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Purpose: ERGs are traditionally recorded using corneal electrodes, which can be difficult for some to tolerate. Recently, a new type of adhesive skin electrode has been introduced which may be better tolerated. We reported on the clinical usefulness of qualitative interpretation of ERG recordings using skin electrodes for a wide spectrum of retinal disorders at the 2017 ISCEV

Symposium. Here we report results of a prospective quantitative comparison of simultaneous ERG recordings using contact lens and adhesive skin electrodes to compare the differences in signal strength.

Methods: The study was Institutional Review Board approved. Twenty patients were enrolled by one retina specialist at the Icahn School of Medicine at Mount Sinai, referred for ERG testing for multiple clinical indications. Informed consent was obtained from patients or their accompanying parent. ERGs were obtained according to ISCEV standards. ERGs were recorded simultaneously from both eyes with ERG-jet® corneal contact lens electrodes and LKC Technologies® Sensor Strip skin electrodes using multi-channel instrumentation (Diagnosys LLC, Espion-3). A-wave and b-wave amplitudes were compared between the two electrode types.

Results: Waveform morphologies obtained with skin electrodes were similar to those obtained with contact lens electrodes. The range of mean ratio of amplitudes for the right eye skin electrode to right eye contact lens electrode ranged from 0.37 to 0.54, with standard deviation (SD) from 0.19 to 0.50. The mean ratio of left eye skin electrode to left eye contact lens electrode amplitudes ranged from 0.34 to 0.42 (SD 0.16–0.40). The grand average of the response amplitude ratios between skin and contact lens electrodes for all test conditions was 0.42 (SD 0.25) for right eyes and 0.38 (SD 0.24) for left eyes. Correlations between amplitude ratios for right and left eyes ranged from 0.26 to 0.70 for the various stimulus conditions, with an overall correlation of 0.419 for all conditions combined.

Conclusions: The ERGs recorded with skin electrodes had smaller amplitudes than ERGs recorded with corneal electrodes but were similar in waveform. Amplitudes obtained with skin electrodes were on average about 40% of those obtained with contact lens electrodes, but the variability of the amplitude ratio is substantial, and correlation between right and left eyes is only fair. Skin electrodes may be a useful alternative method of recording ERGs, especially in children and patients less able to tolerate traditional corneal contact lens electrode ERG testing, particularly if quantitative interpretation is not critical.

5.02 Steady-state PERGs and short-duration pattern VEPs in normal healthy eyes

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Purpose: We evaluated two office-based electrophysiological diagnostic tests, steady-state PERG (ss-PERG) and short-duration transient pattern VEP, in normal healthy eyes to establish repeatability of test results.

Methods: We used a Diopsys® Nova testing system, using standard protocol and skin electrodes, PERG optimized for glaucoma screening (PERGLA) stimulus, followed by ISCEV standard PERG, pattern VEP and full-field ERG in 30 normal healthy eyes. Ss-PERG parameters measured were MagnitudeD; MagnitudeD:Magnitude ratio, and signal-to-noise ratio (SNR). MagnitudeD represents the amplitude of the ss-PERG signal and is highly influenced by its phase consistency. MagnitudeD:Magnitude ratio is a ratio that is a within-subject representation of the phase consistency of the ss-PERG. The short-duration VEP parameters for both low and high contrast stimuli required a reliability index of ≥80% for each eye, and if this was reached, the short-duration VEP testing was complete.

Result: Six eyes were excluded from analysis due to poor patient cooperation or co-existing retinal/optic nerve pathology. Of the 24 patients (48 eyes) analyzed, 15 were males and 9 females, mean age 38.9 years; 17 patients were myopic. For ss-PERG (16° and 24°), 296 repeat tests were performed (average tests per patient n=12) with 91% quality tests. MagnitudeD:Magnitude ratio and SNR were analyzed. For short-duration pattern VEP, 200 repeat tests were performed with 90% quality tests. Mean P100 peak time was not significantly different between low and high contrast stimuli (101.8 ms vs 94.3 ms); however, mean amplitude for high contrast stimuli was larger compared to low contrast stimuli (12.9 μV vs 7.7 μV).

Conclusions: The clinical usefulness of new technologies relies on high test-retest repeatability. Test-retest repeatability of ssPERG

and short-duration VEP using a novel, office-based, testing platform ranged from good to excellent for all tested parameters intrasession. As with all other new technologies, there is a learning curve; therefore, to acquire good quality responses, it is recommended to increase the number of repeat tests (intrasession as well as intersession) for comparison.

5.03 Comparison of cathode-ray tube (CRT), organic light-emitting diode (OLED) and luminance feedback technologies (LFT) for the generation of pattern ERG and VEP stimuli

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Purpose: After 10 years of discontinuation of CRT manufacturing, an alternative solution is needed for the generation of pattern ERG and VEP stimuli. The purpose of this study was to compare OLED and LFT technologies to CRT, both in terms of stimulus properties and in recorded pattern ERGs and VEPs.

Methods: Stimulus luminance and time response were recorded on the three types of stimulators with a fast light sensor. Pattern ERGs and VEPs were obtained to different pattern sizes on five normal subjects. Test distance was 1 m for CRT and LFT stimulators but had to be increased to 2 m for the OLED stimulator due to the size of the monitor.

Results: We found timing differences between the three technologies tested. All achieved a significant reduction of the transient luminance artefact as recommended by ISCEV. However, variable delays of up to 18 ms were recorded between the stimulus command and the light response with the OLED technology. The pattern ERGs and VEPs recorded with the three technologies are identical except for higher amplitudes with the OLED stimulator.

Conclusions: CRT, LFT, and OLED technologies provided stimuli without transient luminance artefacts and evoked similar pattern ERGs and VEPs. However, the variable delay with OLED stimulation needs to be compensated in order to achieve reliable measurements of latency.

5.04 Recording electrical potentials of the ciliary muscle during accommodation

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Purpose: Accommodation is the ability of the eye to change the refractive power of the lens to maintain a focused image on the retina. The classical theory of accommodation proposes that the ciliary muscle (CM) releases tension on the anterior zonular fibers and allows the lens to thicken, thereby increasing the optical power of the lens. Although the anatomical structure of the CM has been well-studied, little is known about its electrophysiological properties. Here we introduce a novel bipolar contact lens electrode that allows for recording the electrical potentials of the CM during accommodation.

Methods: Ten healthy emmetropic subjects (22–28 years old, refractive error <±0.5 D) with high accommodative range (>6 D) were recruited and gave written, informed consent. The study was approved by the local ethics committee and followed the tenets of the Declaration of Helsinki. Two concentric gold rings were sputter-coated on commercially available scleral contact lenses (Ø 20 mm, Boston® XO2, Bausch & Lomb GmbH, Heidelberg, Germany) to record electrical potentials along the radially-oriented zonular fibers. Accommodation was triggered in one eye using a visual target pathway consisting of endo-illuminated perspex plates engraved with the letter "E" at five distances (5, 3.5, 2.5, 2, 0.5 D), while the electrical CM activity was recorded in the contralateral eye using an Espion e² system (Diagnosys Ltd., Cambridge, UK). Targets were presented for 15 s each, alternating between far target (0.5 D) and one of the near targets. To confirm the CM as the source of the potentials, the test was repeated using pharmacological agents to

block pupil (phenylephrine) and CM (cyclopentolate) activity, respectively. Root mean square (RMS) amplitudes were calculated from the average of four sweeps for each target distance in two time intervals: 0–9 s (0.5 D, baseline) and 14–25 s (accommodation) and normalized per subject to the maximum value of all distances.

Results: A one-way analysis of variance (ANOVA) showed a significant effect of the target distance on the normalized RMS amplitude [$F(4, 40)=9.0698$, $p<0.000$]). Post hoc comparison using Tukey's HSD test revealed a statistically significant difference between the mean normalized RMS amplitudes of 0.5 D and 2.5 D ($p=0.033$), 3.5 D ($p=0.0004$), and 5 D ($p<0.001$). Application of phenylephrine showed no effect, whereas the electrical potentials vanished with cyclopentolate.

Conclusions: With the help of improved measurement methods, our aim in this study was to apply the modern technique of electrophysiology to the ciliary muscle and its function, in an attempt to determine its characteristics non-invasively in human eyes. This work describes the development of the novel contact lens electrode and the results obtained in healthy emmetropic subjects. Furthermore, it provides a new technique for recording ciliary muscle activity in the human eye, which would be beneficial for further research on accommodation and could potentially be used to control an electrically-driven device for continuous refractive correction.

Funding: This work was supported by an investigator grant provided by Alcon to E. Zrenner.

5.05 iSim: a standardised methodology for the quality assurance of recording regimes across clinical laboratories

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Purpose: Modern bio-amplifiers used in clinical visual electrodiagnostics are a hybrid of analogue hardware and digital processing software functions. Calibration of such amplifiers must account for the noise environment and ideally be referenced to an internationally recognised calibration standard. This characterisation and calibration is not trivial requiring an informed understanding of the subtleties of signal-to-noise (SNR) enhancement and rejection of recording artefacts. However, the performance characteristics of these devices are specified only notionally by ISCEV making it challenging to establish true reference norms across clinical laboratories using equipment from different manufacturers. The iSim smart ERG and VEP simulator has been developed to non-naively address this challenge.

Methods: The iSim hardware consists of an ARM microprocessor, a multi-channel 16-bit D-to-A converter, and a very-low-noise voltage amplifier with a passband of [0.1 … 500] Hz and a balanced output impedance of 4.7 kOhm. The zero-noise gain is set with respect to an NPL (National Physical Laboratory www.npl.co.uk) secondary standard. The iSim software comprises three elements: i. a library of ISCEV standard ERG and VEP signals; ii. a composite noise model consisting of a 'continuous' ARMA noise source derived from clinical recordings and a 'discontinuous' noise source simulating spontaneous eye movement and blink artefacts; iii. a simple user interface to an operating system which allows the user to select standard ERG and VEP waveforms and the power and composition of the noise component.

Results: A clinical instrument can be characterised and calibrated using the standalone iSim for scotopic ERG, photopic ERG, PERG and flash VEP over discrete SNR's of 6, 0 and -6 dB in ~30 minutes.

The presentation will include a video demonstration of an iSim session.

Conclusions: The iSim ERG signal generator provides highly realistic clinical test recordings. It is suggested that such a device might be of use in calibration within quality control systems and alignment of recording regimes across clinical laboratories. ISCEV might take the lead in developing a programme of clinical and technical governance in visual electrodiagnostic testing by recommending a standard test protocol using a standard panel of test signals delivered by iSim. We are pleased to be able to offer iSim

instruments at cost price to ISCEV colleagues from July 2018.

Funding: We gratefully acknowledge the receipt of Marmor Initial and Follow-up Awards for Clinical Innovation to support the development of iSim.

Thursday 21st June 2018, 11:00–12:45

Session 6: Paper Session — All over the retina

6.01 The slow light and dark oscillation of the clinical EOG

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Purpose: The standing potential of the eye exhibits a slow, damped oscillation under light and dark conditions that continues for at least 80 minutes. However, our understanding of the relationship between the slow dark and light oscillation has not been studied previously. The aim of this study was to explore through regression analysis a model of these oscillations in order to establish if they may have the same underlying cellular generators.

Methods: Healthy participants undertook recordings of the standing potential using the EOG for 100 minutes. To explore the light oscillation, subjects (n=8) were dilated and performed an extended EOG protocol consisting of 15 minutes dark adaptation and 85 minutes of white light adaptation at 100 cd/m^2. For the dark oscillation, subjects (n=11) undertook the EOG for 100 minutes in complete darkness. Both sessions began with pre-adaptation to a white light of 30 cd/m^2 for 5 minutes. Non-parametric statistics were used to evaluate all data.

Results: Ratios of the dark and light oscillations showed a significantly greater dampening of the dark oscillation compared to the light oscillation ($p<0.000$). Regression analysis using a five-factor damped sine function revealed significant differences in the parameters governing the dampening ($p<0.005$) and period ($p<0.009$) of the functions ($R^2>0.874$). There were no significant differences in the dark trough amplitude.

Conclusions: The results support a different underlying physiological mechanism for the light and dark oscillation of the clinical EOG. Future work is necessary to establish how the dark oscillation and dark trough of the clinical EOG arise.

6.02 Tolerability, reliability and clinical efficacy of the RETeval® hand-held light-adapted 30 Hz flicker ERG in awake infants in monitoring retinal side effects of vigabatrin treatment

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Purpose: The RETeval® (LKC Technologies, Gaithersburg, MD, USA) is a non-invasive, hand-held ERG system not requiring dilation and using skin electrodes for ERG assessment. The aim of this prospective, observational study was to evaluate the tolerability, reliability (intra-visit reproducibility) and clinical efficacy of the RETeval® light-adapted 30 Hz flicker ERG in awake infants treated or about to be treated with vigabatrin.

Methods: After parental/guardian informed consent, 28 children with the childhood epilepsy, infantile spasms, were recruited during their appointment at the Sick Kids Ophthalmology clinic. These children were either undergoing or expected to begin vigabatrin treatment. After a series of standard clinical visual assessments by an orthoptist, the children were sedated for clinical ERG testing to monitor for retinal toxicity. All children were ≤ 36 months old. Whilst awake, a

RETeval® ERG was attempted using the protocol 85 Td s, 28.3 Hz flicker with an 848 Td background. Tolerability was identified if RETeval® testing was possible. Two repetitions were attempted on each eye for later assessment using the within-visit intraclass correlation coefficients (ICC) to identify reproducibility of RETeval® ERGs. Following RETeval® ERGs, the children had their pupils dilated and were sedated (chloral hydrate), and standard full-field ERGs (Espion E2 Color Dome, Diagnosys LLC) using corneal jet electrodes, including a light-adapted 30 Hz flicker ERG at 3 cd s/m^2, were recorded. Clinical efficacy was evaluated descriptively using Pearson's correlation coefficient (PCC) between equivalent ERG 30 Hz testing with the RETeval® and with routine, sedated ERGs.

Results: Nine of the recruited 28 children, age range 6–27 months, completed RETeval® 30 Hz flicker ERGs during the first visit. Seven of these (78%) completed the intra-visit assessments with at least one eye having two repetitions of the flicker ERG. Four of the nine participants completed one follow-up visit with RETeval® flicker ERGs, and one child was successfully assessed on three consecutive visits (one baseline and two follow-up visits). Fourteen eyes from seven participants provided two repetitions for intra-visit ICC calculations. The intra-visit ICC for the RETeval® light-adapted 30 Hz flicker ERG amplitude was 0.83. This ICC value represents good reliability. The amplitudes of the RETeval® flicker ERGs showed a strong positive correlation (PCC=0.8, R^2=0.64) with routine, sedated flicker ERG amplitudes.

Conclusions: In this cohort, tolerability was poor, although if the first recording was possible the repeat test was usually successful. The non-compliance is partially explained by previous fasting for sedation which would inevitably reduce the compliance for any test including the RETeval® ERG. RETeval® ERGs were undertaken during the children's routine appointment to assess vigabatrin toxicity and testing was limited to a maximum of 5 minutes, including encouragement if the child was moving, irritated, crying or sleeping. RETeval® data were collected from only nine children which limits the power of these findings. Notwithstanding this caution, results suggest the RETeval® ERG is a reliable technique with clinical efficacy.

6.03 Full field ERG features of East Asian patients with occult macular dystrophy (Miyake's disease); EAOMD Report No. 2.1

Lizhu Yang[1,2,3]*, Kwangsic Joo[4]*, K. Tsunoda[1], M. Kondo[5], Y. Fujinami[1,2,6], G. Arno[1,7], T. Kurihara[2], K. Tsubota[2], T. Iwata[8], Xuan Zou[3], Hui Li[3], Kyu Hyung Park[4], Y. Miyake[1,9], Se Joon Woo[4], Ruifang Sui[3], K. Fujinami[1,2,7]

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Purpose: To describe the characteristic features of full-field ERGs of East Asian patients with occult macular dystrophy (OMD) based on spatial functional phenotypes.

Methods: Patients with a clinical diagnosis of OMD and harbouring pathogenic RP1L1 variants (i.e. Miyake's disease) who underwent recording of mfERGs and full field ERGs were enrolled from three centers in Japan, China, and South Korea (East Asia Inherited Retinal Disease Consortium). Full field ERGs and mfERGs were recorded according to the ISCEV standards. Patients were classified into three mfERG functional groups according to the previous study: Group 1—paracentral dysfunction with relatively preserved central/peripheral function; Group 2—homogeneous central/paracentral dysfunction with preserved peripheral function; Group 3—gross dysfunction over the recorded area. The amplitude (A, μV) and peak time (T, ms) of full field ERG components were investigated. With reference to normal values (N), reduction rate of

amplitude (R=(N-A)/N) and peak time shift (S=T-N, ms) were calculated and statistical comparison was performed between groups.

Results: Twenty two patients (43 eyes) were included in total. There were three, 35, and five eyes in Groups 1, 2, and 3, respectively, with no significant difference in age between groups. The median amplitude reduction/peak time shift (R/S) of the dark-adapted (DA) 0.01 ERG in Groups 1, 2, and 3 were 0.49/16.50, 0.02/5.50, and 0.12/3.90 respectively. The median R/S of DA 3.0 ERG a- and b-waves were 0.81/2.47 and 0.39/4.50; 0.12/0.97 and 0.16/2.60; and 0.14/1.45 and 0.14/5.20, respectively. The median R/S of DA 10.0 ERG a- and b-waves were 0.70/0.55 and 0.89/9.60; 0.10/0.35 and 0.19/5.48; and 0.08/1.45 and 0.17/8.35, respectively. The median R/S of LA 3.0 30 Hz flicker ERG were 0.56/1.61, 0.00/0.00, and 0.26/1.15, respectively. The median R/S of LA 3.0 ERG a- and b-waves were 0.11/0.29 and 0.96/0.89; 0.20/0.15 and 0.02/0.60; and 0.38/0.75 and 0.34/2.05, respectively. A significant difference was revealed between Groups 1 and 2 in amplitude reduction of the DA 0.01 ERG b-wave. There were significant differences between Groups 1 and 3 in peak time shift of the DA 0.01 ERG b-wave, amplitude reduction of the LA 3.0 30 Hz flicker ERG, and amplitude reduction of the LA 3.0 ERG b-wave. Between Groups 2 and 3, a significant difference was found in peak time shift of the DA 10.0 ERG a-wave. All ERG components of Group 1 were considerably larger than those of normal reference.

Conclusions: The full-field ERGs of OMD patients are generally within the normal range; however, patients with gross dysfunction tend to show more decreased amplitudes of light-adapted ERGs. These findings are in keeping with the predominantly localized cone system affected in OMD (Miyake et al. 1996). Interestingly, the full-field ERGs of Group 1 OMD patients were larger than the normal reference; this finding should be further investigated in a larger number of patients.

6.04 The clinical features of cancer-associated retinopathy in a cohort of Chinese patients

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Purpose: Cancer-associated retinopathy (CAR) is a form of autoimmune retinopathy related to systemic cancer. The objective of this study was to analyze the clinical features of CAR.

Methods: This was an observational case series study. Ten patients diagnosed with CAR within five years were enrolled. All patients underwent detailed ocular examinations including ERGs, optical coherence tomography (OCT), visual fields and autofluorescence (AF).

Results: The primary malignancies were lung carcinoma (3/10), thymoma (3/10), thyroid carcinoma (1/10), maxillary sinus tumor (1/10), nasopharyngeal carcinoma (1/10) and rectal cancer (1/10). All patients complained of progressive visual loss. Three patients also manifested night blindness. Three eyes (15 %) showed best corrected visual acuity (BCVA) < 0.1; seven eyes (35 %) had BCVA ≥ 0.1 but < 0.5; and 10 eyes (50 %) had BCVA ≥ 0.5. Most patients showed normal fundi or mild abnormality. OCT images showed disorganization and/or loss of the ellipsoid zone in the macular area in four patients and in the other six patients only the central foveal ellipsoid zone was preserved. Eight patients had moderately or severely reduced full field ERGs, and two patients demonstrated electronegative ERGs. Five patients revealed peripheral visual defects. Patients' AF images varied from normal to low or high AF patches in the posterior pole and mid-peripheral retina.

Conclusions: The clinical manifestations of CAR are varied, with common characteristic features of progressive visual decrease with or without night blindness, visual field defects and abnormal full field ERGs.

6.05 Does unilateral retinopathy pigmentosa exist? Report of four cases

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Purpose: To manage the follow-up of unilateral retinopathy pigmentosa to confirm the diagnosis and to discuss its etiologic opinions.

Methods: Four cases of unilateral retinopathy pigmentosa were selected according to their similar unilateral anatomic and functional ocular anomalies. Full field ERG, mfERG, multimodal imaging, visual field, visual acuity and genetic testing were performed.

Results: Three women and one man, ranging from 25 to 33 years old, were studied. In all cases their visual acuity was bilaterally optimal. In contrast, their visual field was unilaterally very constricted, along with a strict unilateral decrease of both full field ERG and mfERG. Their fundus appearance was also characterized by strict unilateral anomalies, ranging from narrowed retinal vessels, mottling and granularity of the retinal pigment epithelium, migration of pigment in various sizes of clumps or bone spicule formations, atrophy of the retinal epithelium to papillary atrophy. Fundus autofluorescence imaging revealed unilateral central and midperipheral autofluorescence signal decrease, associated with an abnormal parafoveal ring arc of increased autofluorescence. Spectral domain optical coherence tomography scans showed one-sided photoreceptor disruption; cystoid oedema was described in one case. Infectious, neoplastic, and vascular causes were excluded for all four patients, but one had a possible history of eye trauma. Genetic test results are pending. We consider the etiologic hypotheses from the literature where mosaïcism or somatic mutations are discussed.

Conclusions: Unilateral retinopathy pigmentosa is a rare tapeto-retinal dystrophy affecting strictly only one eye, the fellow eye being completely unaffected. All infectious, traumatic, vascular and neoplastic causes have to be excluded and a long visual electrophysiologic follow-up is required for this diagnosis where mosaïcism or somatic mutation may be suspected.

6.06 Comparing corneal and skin electrode recording in ERGs

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Purpose: Recording the ERG with corneal electrodes remains challenging for both patients and clinical staff, especially in children. Skin electrodes have been developed in order to increase the patient's comfort during ERG recording. However, corneal electrode recording of the ERG remains the gold standard in many centers. The present study aimed to compare qualitatively and quantitatively the results obtained with the two types of electrodes.

Methods: A total of 12 consecutive paediatric patients treated with vigabatrin were included in the study. According to the age of the patient, two different stimulation methods were used: either a portable handheld device or a ganzfeld stimulator. The recordings were first performed with skin electrodes, then the corneal electrodes were placed on the eye, and a second set of recordings was done. The highest peak to trough amplitude of the LA 3.0 flicker ERG was considered for the comparison.

Results: The amplitude of the responses was lower with skin electrodes; in two patients they could not be analyzed. The mean ratio between the peak to peak amplitude of the LA 3.0 flicker ERG obtained with corneal electrodes and with skin electrodes varied between 1.9 and 3.2. The mean amplitude obtained with corneal electrodes varied between 45.8 and 63.7 µV; with skin electrodes, it varied between 19.8 and 27.1 µV.

Conclusions: The variability of the cornea/skin electrode ratio did not enable determination of a reproducible conversion rate between the two recording procedures in clinical practice. However, as the lowest measured ratio was near 2, if the skin electrode ERG reaches 50% of the normal amplitude obtained with corneal electrodes, then it is reasonable to consider this as being in the normal range.

6.07 Experiences with electronic Retina Implant Alpha (RI-ALPHA) in more than 60 blind patients with inherited retinal dystrophies

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Purpose: A survey will be given on the safety and efficacy of the subretinal electronic implant Retina Implant Alpha (RI-ALPHA) applied in patients with end stage hereditary retinal dystrophies (IRDs) as assessed in three prospective clinical trials and by tests and observations after commercial approval since 2016, including benefit in daily living.

Methods: The subretinal visual prosthesis RI-ALPHA (Retina Implant AG, Reutlingen, Germany) consists of a microchip 3.2×4 mm in size, 70 µm thick, equipped with 1600 photodiodes to be implanted subfoveally in blind IRD patients, powered by a small, pocket-based power supply via a retroauricular coil. RI-ALPHA devices have been implanted in more than 60 blind patients with IRD either in clinical trials with a follow-up period of 12 months (NCT01024803 and NCT02720640; Zrenner E. et al *Proc Biol Sci* 2011;278:1489; Stingl K. et al *Vision Res* 2015;111:149; Stingl K. et al *Front Neurosci* 2017;11:445; Edwards T.L. et al *Ophthalmology* 2018;125:432) or commercially after availability in the German health care system. Functional outcome measures included 1) screen-based standardized 2- or 4-alternative forced-choice tests of light perception, light localization, grating detection [basic grating acuity (BaGA) test] and Landolt C-rings; 2) grey level discrimination; 3) performance during activities of daily living (ADL-table tasks), and patient reported outcome (PRO). The implant can be applied to adult IRD patients who have no light perception (NLP) or light perception (LP) without light localization, whose inner retinal layers are discernible on OCT, and who were able in childhood to read.

Results: Implant-mediated light perception with the actual marketed version RI-ALPHA AMS was observed in a recent 12 month multicenter clinical trial in 13 out of 15 patients (Stingl K. et al *Front Neurosci* 2017;11:445; Edwards T.L. et al *Ophthalmology* 2018;125:432). Two patients were able to distinguish Landolt C-rings of 20/1111 and 20/546, respectively. Twelve patients could achieve a basic grating acuity between 0.1 and 3.3 cpd. Detection, localization, and counting of objects was significantly better with the implant "ON" than with the implant "OFF" during the whole observation period. On average, 4.6 of six different grey levels could be distinguished. Visual perception was stable during the observation period of 12 months after surgery. The maximum implanted time of a still functioning RI-ALPHA AMS device so far is 48 months. The predicted lifetime of the implant is about 5 years. Patients have experienced benefit in daily life, can localize and discern objects, report spontaneously discovering items in the environment (e.g. dogs wagging their tail, trees, obstacles along the way, even letters in some cases). Some patients were able to locate or see balls on a billiard table, outlines of windows and doorways, metallic kitchen appliances (e.g. kettle and toaster), black and white laundry items, the outline of a mountain against the setting sun, a passing car, Christmas lights, and building edges. The device was also helpful for determining the ambient light level (e.g., whether it was a bright or cloudy day) or when there was shade (e.g., walking under an overhanging tree). Examples will be given of how the implant positively affects the patients in their daily life. Serious adverse events (SAEs) were reported in four patients: two movement of the implant, readjusted in a second surgery; three conjunctival erosion/dehiscence, successfully treated; one pain event around the coil, successfully treated; one partial reduction of silicone oil tamponade leading to distorted vision (silicon oil successfully refilled). The majority of adverse events (AEs) were transient and mostly of mild to moderate intensity.

Conclusions: Psychophysical and subjective data show that RI-ALPHA AMS is safe, reliable, well tolerated, and can restore limited visual functions in blind patients with degenerations of the outer retina. Longevity of the new implant RI-ALPHA AMS has considerably improved, with an expected mean life time of 5 years. RI-ALPHA AMS has been certified as a commercially available medical device, in Germany reimbursed by the public health system.

Session 7: Paper Session — Animal: clinical and pre-clinical

7.01 The dynamics of rod and cone driven ERG adaptation to high and low luminances

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Purpose: We previously described the adaptation dynamics of ERGs to high and low luminances. However, we did not allocate these dynamics to changes in rod or cone driven pathways. By using the physiologically normal *Opn1lw*^{LIAIS} (LIAIS) mouse, in which the native M-cone pigment is replaced by a human L-cone pigment, it is possible to stimulate selectively the rods or the cones with the silent substitution stimulation technique. We used the silent substitution technique in the LIAIS mouse to study separately cone and rod driven adaptation dynamics.

Methods: ERGs were recorded from anesthetized LIAIS mice. Stimuli for ERGs: sinusoidal isolated rod (8 Hz, 75% rod contrast) or cone (12 Hz, 55% cone contrast) modulation using the double silent substitution; S-cones were always silenced. Responses to luminance stimuli (8 Hz and 12 Hz; 100% Michelson contrast) were measured. Procedure: (1) After 10 minutes adaptation to a 0.4 cd/m² white background, rod and cone driven and luminance ERGs were recorded. (2) After 11 minutes adaptation to a 8.8 cd/m² white background, rod and cone driven and luminance ERGs were recorded directly after the change in background and every 2nd minute. (3) After 32 minutes adaptation to a 0.4 cd/m² white background, rod and cone driven and luminance ERGs were recorded directly after the change in background and every 2nd minute.

Results: At 8.8 cd/m², responses directly displayed photopic response properties without subsequent response changes in either cone or white light responses. Rod driven responses were very small. 12 Hz white light responses had similar characteristics to the cone driven responses. After the return to 0.4 cd/m², both rod driven and white light responses increased over a time course of about 20 minutes. The 8 Hz white light responses were similar to the rod driven responses. Cone driven responses were very small. Response phases changed directly after a change in background with small alterations only in rod driven responses.

Conclusions: Rod and cone driven signal pathways displayed different adaptation characteristics: Adaptation of cone driven responses to low photopic conditions was instantaneous. After a change to scotopic conditions, rod driven responses change with a time course of several minutes. Responses to white light were cone driven at 8.8 cd/m² and rod driven at 0.4 cd/m².

7.02 Dogs lacking the cyclic nucleotide-gated channel beta-1 subunit (Cngb1) have residual desensitized rod function prior to photoreceptor degeneration

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Purpose: The rod cyclic nucleotide-gated channel is a heterotetrameric structure consisting of three alpha and one beta subunit and is essential for light-induced rod photoreceptor signalling. The dark-adapted ERG of dogs with a null mutation in the gene encoding the beta subunit (Cngb1) fails to mature normally and has an elevated threshold and reduced amplitude. Cngb1$^{-/-}$ dogs are blind at low lighting levels and develop a rod-led photoreceptor degeneration, thus closely mimicking retinitis pigmentosa type 45. Cone-mediated responses are initially normal and only slowly decline. This study aimed to investigate the residual ERG of Cngb1$^{-/-}$ dogs prior to photoreceptor degeneration.

Methods: Dark-adapted, light-adapted, flicker, and chromatic ERGs were recorded from Cngb1$^{-/-}$ puppies from 3 weeks of age. These were compared with ERGs from puppies with a null mutation in the rod cyclic GMP phosphodiesterase alpha subunit (Pde6a) and phenotypically normal littermates heterozygous for the mutations.

Pde6a$^{-/-}$ puppies have a failure in rod phototransduction and lack rod-mediated ERG responses but prior to retinal degeneration have relatively normal cone function. Immunohistochemistry (IHC) was used to identify alpha and beta CNG subunits in the retina of Cngb1$^{-/-}$ puppies.

Results: Between 3 and 5 weeks of age, the response threshold and amplitudes of dark-adapted and light-adapted ERGs of Cngb1$^{-/-}$ puppies were very similar, indicating a lack of rod responses. However, by 7 weeks of age, although response thresholds remained similar, a second slow positive waveform became apparent in only the dark-adapted ERG. With increasing stimulus strength, this delayed waveform increased in amplitude and shortened in implicit time. In response to stronger stimuli, it appeared to merge with the initial b-wave, resulting in a combined waveform of greater amplitude that was considerably broader than that of the matched light-adapted response. This additional positive waveform was present in response to blue flashes but not red flashes. Pde6a$^{-/-}$ puppies acting as a control for a complete absence of rod function had dark- and light-adapted responses that were similar in amplitude and shape at all ages. IHC of Cngb1$^{-/-}$ retinas confirmed the absence of full-length Cngb1 and revealed a low level of Cnga1 in rod outer segments.

Conclusions: Cngb1$^{-/-}$ puppies lack normal rod function. Taken together, the ERG results suggest that they do show a developmentally delayed, desensitized, and reduced rod-mediated response. The IHC findings indicate that this abnormal rod response may be possible because of the formation of a low number of Cnga1 monotetrameric channels in the rod outer segments. CNG channels lacking Cngb1 would be expected to have altered dynamics due to a lack of the modulating effect of Cngb1 but allow some signalling to second order neurons.

Funding: Myers-Dunlap Endowment for Canine Health, Papillon Club of America

7.03 A pharmacological approach for retinitis pigmentosa

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Purpose: Rhodopsin (RHO) mutations are responsible for 25–40% of the dominant cases of retinitis pigmentosa (RP) with distinct amino acid substitutions causing different RP severity and progression rates. Tvrm4$^{/+}$ mice, heterozygous for a I307N dominant mutation of RHO, display a normal retinal phenotype when raised in ambient light conditions but undergo photoreceptor degeneration when briefly exposed to strong white light. We induced a retinal degeneration in Tvrm4$^{/+}$ mice and treated the animals with intra-vitreal or intraperitoneal injections of Myriocin, a serine-palmitoyl-transferase inhibitor shown to delay retinal degeneration in rd10 mice, mimicking recessive RP.

Methods: Tvrm4$^{-/+}$ mice aged 2–4 months were given eye drops of atropine, placed in a custom-made illuminating box, and exposed to two minutes of 12,000 lux white neon light. Twenty four hours after induction of the degenerating process, animals were given one intravitreal injection of Myriocin (1.87 mM). The contralateral eye was injected with an equal amount of vehicle (DMSO) and served as control. Intraperitoneal administrations (1 mg/kg daily for four days) were started the same day as light induction; an equal amount of vehicle was given to a control group of mice. Subsequently (24 hours after the drug delivery), retinal functionality was tested by recording flash ERGs in both scotopic and photopic conditions. Retinal tissue was collected from recorded mice at the end of the electrophysiological tests. The tissue was used for further analyses including morphological, biochemical, and liquid chromatography–mass spectrometry assays.

Results: Light-induction of Tvrm4$^{/+}$ mice triggered a typical rod-cone degeneration in an area concentric to the optic disc. Rod outer segments shortened after 48 hours. Cones degenerated more slowly. Mice treated with Myriocin showed a) a decreased number of apoptotic cells and a reduction of the damaged retinal area; b) lowered retinal levels of de novo synthesized ceramide

species; c) a substantial improvement of both scotopic and photopic ERGs; and d) a marked reduction of the expression of oxidative stress markers in the retina.

Conclusions: Intravitreal and intraperitoneal delivery of Myriocin is effective in counteracting photoreceptor degeneration, possibly by inhibiting the de novo synthesis of ceramide and reducing oxidative stress. Combined with previous results on rd10 mutants, the present results demonstrate that Myriocin slows the degeneration process both in a phosphodiesterase, recessive mutation and in a rhodopsin, dominant model of RP. The mutation-independent efficacy of this molecule opens encouraging perspectives for the pharmacological treatment of the disease.

Funding: Fondazione Roma (Italy)

7.04 A novel therapeutic concept in Pde6-related retinitis pigmentosa

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Purpose: Loss-of-function mutations in Pde6 genes lead clinically in most cases to retinitis pigmentosa (RP). The onset of the disease in rod photoreceptors has been attributed to either a massive increase in cyclic guanosine monophosphate (cGMP) or a presumed deviation of the Ca^{2+} metabolism. Although specific therapeutic approaches based on adeno-associated virus-mediated gene delivery show first promising results in genetically homologous models of the human disease such as rd1, the underlying pathophysiology has not yet been satisfactorily resolved. Therefore, the aim of this work was to gain insight into the disease mechanisms by distinguishing between (a) the direct impact of the intracellular rise in cGMP levels, and (b) presumed Ca^{2+}-related effects mediated by rod cyclic nucleotide gated (CNG) channels in the outer segment membrane, and to develop a therapeutic strategy on the basis of these findings.

Methods: Pde6a and Pde6b preclinical models of cGMP-related RP were cross-bred with Cngb1 knockout mice (B6.129SvJ-Cngb1tm) lacking rod CNG channels. These DKO lines include: (1) rd1/Cngb1 (B6.129SvJ;C3HeB/FeJ-Pde6brd1/rd1-Cngb1tm) (2) V685M/Cngb1 (A.B6-Tyr+/J-Pde6anmf282/nmf282-Cngb1tm), and (3) R562W/Cngb1 (A.B6/J-Pde6aR562W/R562W-Cngb1tm). Lines were evaluated in vivo using non-invasive diagnostic techniques and in vitro via a histological work-up. The results were compared to those in Pde6 single-mutants and wild-type mice.

Results: The newly generated DKO lines show that a removal of CNG channels from rods by cross-breeding with $Cngb1^{-/-}$ does substantially protect PDE6-deficient models from developing cGMP-related RP. While the outer retina was entirely lost within 15–30 days after birth in unprotected lines, at least one layer of photoreceptor rows remained until 3–6 months in protected lines, an age where the CNGB1 deficiency alone significantly contributes to degeneration. Importantly, cone function in both lines remained detectable until the end of the current study at age 6 months.

Conclusions: The high degree of protection found in the double mutants clearly indicates that the dominant deleterious effect requires functional rod CNG channels. In particular, these findings suggest that the impaired Ca^{2+} influx mediated by CNG channels is causative for disease development. Therefore, a specific modulation of rod CNG channels, but not cone channels, is a most promising symptomatic approach to treat otherwise incurable forms of cGMP-related RP and may also help to widen the therapeutic window for later gene therapeutic approaches.

7.05 Do photopic negative responses (PhNRs) reflect retinal ganglion cell function in chicks?

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Purpose: The anatomy of the chick retina is similar to that of primates but with the notable difference of an absent central retinal blood supply in the former. Furthermore, the chick retina is cone-rich and grows rapidly. Photopic negative responses (PhNRs) of flash ERGs reflect retinal ganglion cell (RGC) function in primates. This study was undertaken to determine if PhNRs in the chick model reflect RGC function.

Methods: Full field, light-adapted ERGs were recorded from the eyes of six hatchling chicks (day one) to 4 ms red flashes (LED with peak λ=650 nm) in increasing 0.5 log steps from 0.1 to 8 cd s/m² on a rod-suppressing blue (λ=462 nm) background (30 cd/m^2). RGC function was blocked one hour before ERG recording, on day three to 21, by intraviteral injection of 0.8 µg tetrodotoxin (TTX) in phosphate buffer solution (PBS) with sham PBS injection in the contralateral eye of each bird. Least squares fitting of Naka-Rushton curves was used to calculate maximum amplitudes (V_{max}) and sensitivity at half V_{max} of the b-waves and the PhNRs, measured from trough to b-wave peak. Comparisons used repeated measures ANOVA with Bonferroni post-hoc corrections.

Results: The PhNRs were recorded in all eyes to flashes above 0.1 cd s/m². V_{max} of the PhNRs did not differ between eyes treated with TTX and control eyes (151.1±11.3 µV vs 164.2±6.9 µV, p = 0.11 across sessions). No other ERG differences were found based on TTX treatment, but both the b-wave and PhNR amplitudes increased significantly between day five and day 14. The PhNRs were relatively small compared with those of primates; PhNRs typically fell slightly below the pre-stimulus baseline for weak flashes and were above baseline for stronger flashes in both treated and control eyes.

Conclusions: The PhNR of full-field ERGs in chicks was small relative to those of primates and did not reflect functional disruption of RGCs by TTX. It is possible that generation of the PhNR is enhanced by the interaction of RGCs with an inner retinal vascular supply.

Funding: Natural Sciences and Engineering Research Council of Canada, University of Waterloo, Ontario Trillium Scholarship

7.06 Photopic ERG and flash VEP in neonatal monkeys with maternal zika virus exposure

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Purpose: Zika virus (ZV) infection during pregnancy is a cause of congenital brain abnormalities, including microcephaly. The purpose of this ongoing study is to determine whether ocular signs of ZV infection can be detected at birth in a non-human primate model. We present initial data from neonatal monkeys from ZV-infected mothers without evidence of infection at the time of testing in order to characterize normal retinal and cortical function in the newborn monkey.

Methods: Four rhesus monkeys whose mothers were infected with ZV were tested within 1 week of delivery. None of the four infants tested positive for ZV in urine or plasma. Viral load assays in infant tissues are in progress. Animals were anesthetized with ketamine and dexmedetomidine, and pupils were dilated. After approximately 10 minutes of light adaptation, testing was performed in a ganzfeld bowl using disposable contact lens electrodes and subdermal electrodes for flash VEP recording. The photopic ERG test conditions include LA 3.0, and LA 30.3 Hz flicker. The flash VEP was the average of 80 flashes at a 4 s^{-1} or a 30 s^{-1} rate.

Results: All infants exhibited a robust and repeatable LA 3.0 ERG notable for containing two peaks, unlike the single photopic peak seen in adult monkeys. The average implicit times for the two photopic peaks in the infant monkeys were ~24.5 and 34.5 ms, respectively, with little variation between animals. Amplitudes ranged from 27 to 52 µV. Young adult monkeys had an average photopic implicit time of 26.6±1.1 ms and an average amplitude of 77.0±23.3 µV. 30 Hz flicker ERGs were also robust in all four infants, but the implicit times were delayed to ~45 ms with amplitudes ranging from 20 to 39 µV. In comparison, adult monkeys' 30 Hz implicit times

are 24.2±1.47 ms with an average amplitude of 93±29.7 μV. The flash VEP recorded from infant monkeys differs markedly from adults in implicit time and amplitude. The newborn monkey flash VEP implicit time ranged from 124 to 130 ms compared with an adult average of 60.5 ms. Along with the marked delay, the amplitude of infant flash VEPs were remarkably large, ranging from 50 to >100 μV. The average adult flash VEP amplitude is 18.0±14.5 μV. When the stimulus rate was 30.3 Hz, infants' flash VEPs were reduced to near-noise levels.

Conclusions: The photopic single flash ERG of the neonatal monkey is robust and repeatable but contains two peaks with implicit times close to that in adults and amplitudes that are approximately half that in adults. Photopic 30 Hz ERGs from infants are delayed, but only slightly reduced in amplitude. The flash VEP from infants is greatly delayed compared with that in adults. The infant monkey also exhibits extraordinarily large flash VEP amplitudes, exceeding five times the adult average, yet are refractory at 30 Hz. These data provide preliminary support for and outline limits to the use of ERG and flash VEP in the early detection of ZV.

Friday 22nd June 2018, 10:00–11:30

Session 8: Paper Session — Clinical retina

8.01 Retinal function in proliferative diabetic retinopathy treated with intravitreal ranibizumab and laser photocoagulation targeted to ischemic retina

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Purpose: To compare panretinal photocoagulation (PRP) as described in the Early Treatment of Diabetic Retinopathy Study (ETDRS) combined with intravitreal injection of ranibizumab (IVR) (ETDRS-PRP group) and retinal photocoagulation targeted to ischemic retina combined with IVR (ISQ-RP) in patients with proliferative diabetic retinopathy (PDR).

Methods: Patients with PDR and no prior laser treatment were randomly assigned to receive either PRP plus IVR ("ETDRS-PRP" group, 15 eyes) or retinal photocoagulation targeted to ischemic areas plus IVR ("ISQ-RP" group, 15 eyes). PRP was administered in two sessions (at weeks 0 and 2) and IVR was administered at the end of the first laser session. Standardized ophthalmic evaluation including ETDRS best-corrected visual acuity (BCVA) and central subfield macular thickness (CMT) measured by spectral domain optical coherence tomography (OCT) were performed at baseline and every 4 weeks through week 48. Area of fluorescein leakage from active neovessels (FLA) was measured by fluorescein angiography every 12 weeks until final visit. Additionally, full field ERGs were recorded at baseline and after 3 months follow-up.

Results: A total of 30 eyes from 22 patients were enrolled, but only 22 completed the 48-week study period, 12 eyes in the ETDRS-PRP group and 10 eyes in the ISQ-RP group. There was no significant difference between groups regarding BCVA, CMT, or FLA at baseline ($p > 0.05$), and there was no relevant change in BCVA or CMT during follow-up. A significant FLA reduction was observed at all follow-up visits compared to baseline for both groups, but there were no differences between groups. The mean number of IVR injections was 8 and 6.25 for the ETDRS-PRP and ISQ-RP groups, respectively. ERGs at baseline showed typical functional changes caused by diabetic retinopathy (reduced dark-adapted OPs and a- and b-wave amplitude, associated with increased b-wave implicit time). These changes were also significantly amplified after laser treatment, with a reduction of 78% of rod b-wave amplitude for group ISQ-RP and 71% for ETDRS-PRP, but there were no between-groups significant differences ($p>0.05$). A similar picture was observed for all ERG parameters.

Conclusions: These data indicate that photocoagulation targeted to ischemic retinal areas associated with IVR is as effective at reducing

active neovessels and led to similar ERG changes as EDTRS-PRP with IVR.

8.02 Comparison between micropulse laser treatment versus intravitreal injection of ranibizumab in diabetic macular edema using mfERGs

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Purpose: To compare the therapeutic effect of intravitreal injection of ranibizumab versus subthreshold micropulse laser (SML) in the treatment of diabetic macular edema (DME), both anatomically by optical coherence tomography (OCT) and functionally by best corrected visual acuity (BCVA) and by mfERG.

Methods: Sixty eyes included in this study were classified into three groups: Group 1 included 20 eyes of 15 patients treated by intravitreal injection of ranibizumab at doses of 0.5 mg in 0.05 ml; Group 2 included 20 eyes of 15 patients treated by SML, and Group 3 was a control group for mfERG which included 20 eyes of 12 patients with diabetes mellitus type 2 of more than 10 years' duration and absence of any signs of diabetic retinopathy.

Results: There was a significant improvement in BCVA before and 3 months after treatment in both Group 1 and Group 2 ($p<0.001$). Also, there was a significant difference between treated groups in BCVA improvement ($p<0.001$); the mean BCVA improvement was 97.6±46.6% in Group 1 and 31±26.1% in Group 2. There was a significant decrease in central subfield thickness before treatment and 3 months after treatment in both Group 1 and Group 2 ($p<0.001$). Also, there was a significant difference between treated groups in terms of decreased central subfield thickness ($p<0.001$); the mean percentage decrease was 33.4±15.6% in Group 1 and 5.8±4.7% in Group 2. There was a significant decrease in OCT macular cube average volume before treatment and 3 months after treatment in both Group 1 and Group 2 ($p<0.001$). Also, there was a significant difference between treated groups in terms of decreased OCT macular cube average volume ($p<0.001$); the mean percentage decrease was 10.6±6.3% in Group 1 and 4.1±4.5% in Group 2. There was a significant improvement in mfERG P1 amplitude before and after treatment in Group 1 ($p<0.002$) but not in Group 2. There was a significant difference between treated groups in terms of P1 amplitude improvement ($p<0.001$); the mean P1 improvement was 16.8±11% in Group 1 and 3.6±9.1% in Group 2. Also, there was a significant difference in P1 amplitude in Group 3 (control) versus both treated groups ($p<0.001$). There was a significant decrease in mfERG P1 implicit time before and after treatment in Group 1 ($p<0.001$) but not in Group 2. Treated groups did not differ in terms of P1 implicit time; the mean P1 implicit time decrease was 5.2±5.6% in Group 1 and 1.4±6.5% in Group 2. Also, there was significant difference in P1 implicit time between Group 1 and Group 3 (control) ($p<0.003$).

Conclusions: Eyes with DME have significantly abnormal mfERG responses. Intravitreal injection of ranibizumab for DME is a superior treatment modality than SML in improving both anatomical and functional results.

8.03 Supernormal flicker ERG amplitudes in eyes with central retinal vein occlusion: frequency, clinical characteristics, prognosis, and effects of anti-VEGF drug

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Purpose: To determine the incidence, clinical characteristics, prognosis and effect of anti-VEGF drugs in eyes with a central retinal vein occlusion (CRVO) associated with supernormal flicker ERG amplitudes.

Methods: One eye in each of 48 patients with CRVO was studied. After full mydriasis, flicker ERGs were recorded from both eyes using the RETeval system. The amplitudes and implicit times of the fundamental component were analyzed. Supernormal flicker ERGs were defined as those

with amplitude larger than 110% of that in the unaffected eye.

Results: Twelve of the 48 eyes (25%) with a CRVO had supernormal flicker ERG amplitudes before treatment. These 12 eyes had implicit times <34 ms, and half of these 12 eyes had implicit times within the normal range. When compared to the other 36 eyes, the eyes with supernormal flicker ERG amplitudes (n=12) had significantly better visual acuity at 1 year after treatment, were more frequently the non-ischemic type, and had less chance of receiving panretinal photocoagulation within 1 year. Interestingly, the eyes with supernormal flicker ERGs had a significant reduction in flicker ERG amplitude after a single injection of an anti-VEGF drug.

Conclusions: These results indicate that a supernormal flicker ERG can be a sign of a mild degree of ischemia, and these eyes have better prognosis. The results also suggest that the supernormal flicker ERG amplitude may be caused by the changes in the electrical activities of retinal cells following mildly increased levels of VEGF in eyes with CRVO.

8.04 The ERG in the early post-operative period in eyes with epiretinal membrane: 3D-system versus eyepiece

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Purpose: In order to study the effect of vitrectomy on the ERG, we recorded the ERG using a skin electrode in early post-operative days in eyes with epiretinal membrane (ERM).

Methods: ERGs were recorded according to the ISCEV standard 1 day, 7 days and 1 month after phaco-vitrectomy. Skin electrodes were used, and pulse reference power line noise reduction system was used for noise reduction. For 10 eyes, the operating microscope with the eyepiece was used, and for 10 eyes, the 3D-system (Ngenuity®, Alcon) was used.

Results: In the 3D-system group, no component of the ERG revealed a significant reduction or delay after surgery. In the eyepiece group however, scotopic b-wave ($p<0.01$), maximum flash b-wave ($p<0.04$), and photopic b-wave ($p<0.04$) and flicker ERG ($p<0.03$) showed a significant reduction one day after surgery, and recovery was observed one week after surgery. In both groups, peak times of all components did not show a significant delay after surgery. We found no significant difference in operation time, visual acuity, or distortion measured 1 week and 1 month after surgery.

Conclusions: We found a transient but significant reduction in some the ERG components one day after surgery in the eyepiece group but not in the 3D-system group. The 3D operating system required less illumination for surgical manoeuvres than the eyepiece system, so we think that this transient reduction was caused in the eyepiece group by higher illumination. Although visual recovery was the same in both groups, the 3D operating system may have some advantages in surgery for severely damaged retinae.

8.05 Influence of internal limiting membrane peeling on macular function in patients treated for macula-on rhegmatogenous retinal detachment

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Purpose: To assess the influence of internal limiting membrane (ILM) peeling on macular function in patients treated for macula-on rhegmatogenous retinal detachment (RRD).

Methods: Eighteen patients with bullous RRD who did not show foveal detachment were recruited

according to the previously presented criteria (Akiyama K. et al. 53rd ISCEV Symposium, 2015). All patients underwent vitrectomy to repair the RRDs. In 12 cases, ILM was peeled during vitrectomy to prevent post-surgical epiretinal membrane growth. The focal macular electroretinogram (FMERG) was recorded at baseline (pre-operatively), 1 month, 3 months, and 6 months post-operatively in the affected eye. A commercially available system (ER80; Kowa, Mayo, Japan) was used for recording; the luminances of the stimulus/background were 115.7/8.0 cd/m^2; the stimulus duration was 100 ms; and the spot size was 15° in diameter. The amplitude and the implicit time of a-wave, b-wave, and OPs were measured. To evaluate the post-operative change of the macular function, each parameter at each post-operative time point was compared to the baseline value using the Wilcoxon signed-rank test. To assess the influence of ILM peeling on macular function, each parameter at each time point was compared between ILM-peeled and ILM-not-peeled cases using the Mann-Whitney U test. Statistical significance was defined as $p<0.05$.

Results: The average age of the 18 patients was 54.5 (SD 5.5) years at baseline. The average amplitudes of each FMERG parameter were as follows (ILM-peeled / ILM-not-peeled cases at baseline, 1 month, 3 months and 6 months, respectively): a-waves 1.33±0.63/1.18±0.21 μV, 1.28±0.37/1.44±0.56 μV, 1.26±0.40/1.39±0.50 μV, 1.52±0.35/1.40±0.21 μV; b-waves 3.08±1.04/3.29±0.69 μV, 3.18±0.68/2.93±0.53 μV, 3.14±0.84/3.42±0.66 μV, 3.63±0.51/3.39±0.52 μV; OPs 0.67±0.20/0.68±0.20 μV, 0.59±0.13/0.74±0.30 μV, 0.55±0.18/0.69±0.03 μV, 0.78±0.36/0.79±0.34 μV. The averaged implicit times of each parameter were: a-waves 20.56±0.89/21.38±0.87 ms, 21.45±0.77/20.62±1.56 ms, 21.38±0.82/20.62±1.56 ms, 20.83±1.06/21.17±1.25 ms; b-waves 39.27±2.08/38.67±2.25 ms, 39.59±3.43/39.30±1.90 ms, 39.67±3.21/40.53±1.03 ms, 38.52±2.30/41.10±1.71 ms; OPs 32.50±1.40/31.96±0.077 ms, 32.29±2.71/32.02±2.22 ms, 31.58±2.42/33.12±0.95 ms, 31.73±1.67/32.84±1.14 ms. Comparison between baseline and post-operative values revealed prolonged implicit time in a-waves at three months in ILM-peeled cases ($p=0.013$) and at 1 and 6 months in ILM-not-peeled cases ($p=0.027$ and $p=0.046$, respectively), and in OP at 3 and at 6 months in ILM-not-peeled cases ($p=0.046$ and $p=0.046$, respectively). None of the other parameters showed significant alterations between baseline and post-operative observations. None of the parameters differed significantly at baseline between ILM-peeled and ILM-not-peeled cases, nor did post-operative evaluation show significant differences between the two groups except that the implicit time of b-waves at 6 months was longer among ILM-not-peeled cases ($p=0.019$).

Conclusions: These FMERG data suggested that ILM-peeling caused no adverse effect on macular function within 6 months post-operatively among patients treated for macula-on RRD.

8.06 High frequency flicker ERG abnormalities in early-stage diabetic retinopathy

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Purpose: To define the nature and extent of abnormalities in the flicker ERG in diabetics who have mild or no non-proliferative diabetic retinopathy (NPDR).

Methods: Light-adapted flicker ERGs were recorded from 20 visually-normal, non-diabetic individuals (aged 51.1±12.1 years), 20 diabetics with no clinically apparent retinopathy (aged 52.6±6.6 years), and 20 diabetics with mild NPDR (aged 54.4±8.6 years). There were no statistically significant differences in mean age among the groups ($F=0.61$, $p=0.55$). ERGs were elicited by full-field sine wave modulation of an adapting field (mean luminance 200 cd/m^2) and recorded using conventional techniques. The field was modulated at temporal frequencies ranging from 8 Hz to 100 Hz in steps of approximately 0.05 log units. Fourier analysis was used to derive the amplitude and phase of the fundamental and harmonic components of the response. Repeated measures analysis of variance (ANOVA) with Holm-Sidak multiple comparisons were used to compare the amplitudes and phases of the control and patient groups across stimulus frequencies.

Results: ANVOA indicated that both patient groups had significant fundamental amplitude reductions for temporal frequencies of 56 Hz and higher (all p=0.03). For frequencies between 56 Hz and 100 Hz, the mean fundamental amplitude was reduced by 34% for the no DR group and by 48% for the mild NPDR group. Both patient groups had significant reductions in the estimated high-frequency response cutoff (i.e. the highest frequency that elicited a measurable ERG): control=118.5 Hz, no DR=103.7 Hz, mild NPDR=98.3 Hz. Response timing, however, did not differ significantly among the groups at any frequency (F=3.06, p=0.06). The amplitude and phase of the high frequency harmonics (32, 48, 64, 80, and 96 Hz) of the patients' responses to slow flicker (16 Hz) were normal, despite the high frequency loss of fundamental amplitude. For example, the mean fundamental response elicited by 62 Hz flicker was reduced by 34% for the no DR subjects, but their 4th harmonic response to 16 Hz flicker (equivalent to 64 Hz) was only reduced by 1% on average.

Conclusions: Diabetics who have mild or no clinically apparent retinopathy can have marked attenuation of the flicker ERG at high temporal frequencies, but the high frequency harmonics elicited by slow flicker were generally normal. This pattern of results can be interpreted within the context of a linear-nonlinear-linear cascade model of retinal processing. The model suggests that the likely site of the abnormal high frequency temporal filtering in diabetics occurs before the harmonic components of the ERG are generated, implicating a photoreceptor origin.

Friday 22nd June 2018, 11:30–12:30

Sponsor session: BAYER

11:30 **Innovation with anti VEGF treatments: is it still possible?**

M. Afriat. Service d'Ophtalmologie, Reims, France

11:45 **Innovation in inherited retinal diseases**

I. Audo, Paris, France

12:00 **Electrophysiological follow-up of chronic diseases**

C. Kamami, Paris, France

12:15 **Clinical cases**

M Afriat[1], C. Kamami[2] I. Audo[2]; [1]Reims, [2]Paris, France

Friday 22nd June 2018, 13:30–15:30

Session 9: Poster Session 2

9.01 Abnormal flash ERGs in patients suffering from Pelizaeus-Merzbacher disease

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Purpose: Our goal was to describe abnormal full-field ERGs found in patients (N=10) suffering from Pelizaeus-Merzbacher disease (PMD, OMIM 312080). PMD is a rare recessive X-linked leukodystrophy leading to hypomyelination of the

central nervous system. It is caused by abnormal expression of the proteolipid protein PLP due to mutations in PLP1 gene. Although numerous studies described abnormal VEPs with increased latency or absence of response related to central nervous system hypomyelination, ERGs have always been reported normal, most probably due to the fact that retinal axons are not myelinated. To our knowledge, no study combining ERG and VEP recordings in PMD patients has been conducted.

Methods: Full-field ERGs and VEPs were recorded on alert patients with natural pupils after verifying that pupil diameter was at least 3 mm. Flash VEPs were first recorded according to ISCEV protocol with active electrodes at O1 and O2 to evaluate the severity of white matter involvement. Three flash ERGs were subsequently recorded with skin electrodes: dark-adapted combined rod-cone standard flash ERG, light-adapted standard flash cone ERG, and light-adapted 30 Hz flicker ERG to verify the normality of retina functioning. All examinations were performed with Metrovision MonPackOne Monitor and portable stimulator at Lariboisière Hospital, Paris (France).

Results: A total of 10 PMD patients (all male) were included. All had well documented PLP1 mutations. Mean age (range) at VEP/ERG recordings was 10.5 (3–25) years. All 10 patients had abnormal VEPs with abnormal waveforms (n=2), or decreased amplitude and delayed peak time (n=5), or non-detectable VEPs (n=3). Seven of the 10 patients had abnormal full-field ERGs. Amplitude of the flicker ERG was decreased (n=1, n° 6); amplitude of the b-wave combined rod-cone ERG was decreased or electronegative with normal cone and flicker ERG (n=3, n° 1, 5, 2), electronegative b-wave of the combined rod-cone ERG with electronegative b-wave of the cone ERG and normal flicker ERG (n=2, n° 8, 9); amplitude of the b-wave combined rod-cone ERG was decreased with non-detectable cone and flicker ERGs (n=1, n° 7).

Conclusions: No study combining ERG and VEP recordings had previously been reported in a series of PMD patients. In addition to abnormal VEPs already described in the literature, we found abnormal ERGs in seven of the 10 subjects studied. These abnormalities mostly involved the inner layers of the neuroretina and cannot be explained only by the primitive hypomyelination described in PMD. We hypothesize a possible retrograde retinal involvement secondary to axon loss in the optic nerve, itself a consequence of the hypomyelination as described in animal models.

9.02 Isolated foveal hypoplasia: study with OCT and OCT angiography

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Purpose: To study retinal vasculature in cases with isolated foveal hypoplasia.

Methods: Three patients (six eyes) were included in the study: an 18 year old male with grade 2 hypoplasia, and a 23 year old male and his 14 year old sister, both with grade 4 hypoplasia and normal PAX6 gene study. All patients had complete ophthalmic examination including ERG, VEP, fundus autofluorescence (FA), ocular coherence tomography (OCT) and OCT angiography (OCTA).

Results: Foveal hypoplasia was graded by OCT, and size of FAZ in superficial and deep retina vasculature was studied by OCTA.

Conclusions: OCTA helps to understand the underlying pathology for different grades of foveal hypoplasia.

9.03 Case report: dynamic visual acuity in bradyopsia

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Purpose: To report a case of the rare hereditary retinal disorder bradyopsia and to describe a method to measure visual function loss that suits the activity limitations experienced in patients with this disorder. Photoreceptors in subjects with bradyopsia have a longer than normal recovery

time resulting in a prolonged electro-retinal response suppression (PERRS). Patient's visual functioning worsens in high luminance conditions with low contrasts. Because in daily life lighting conditions have an enormous variation, functional consequences vary accordingly.

Methods: The patient was a 17 year old male who complained of variable poor vision, light hindrance, and problems with light adaptation and seeing moving objects. He also suffered from headaches and had blurred near and far vision. Visual function testing revealed different visual acuity under different lighting conditions. The ERG (extended ISCEV protocol) showed reduced responses of the light adapted ERG. Dark-adapted ERG for the lower intensities was normal and for the higher intensities was normal after a prolonged recovery time of minutes instead of seconds. Genetic testing showed two pathogenic mutations in RGS9 confirming bradyopsia. We performed the following tests to evaluate the perception of moving and stationary high and low contrast optotypes at different luminance levels (Kooijman AC et al. *Doc Ophthalmol* 1991;78:245; Kooijman AC et al. *Doc Ophthalmol* 2005 poster). The stimuli were optotypes projected with a video projector on a retro-reflective screen with four background luminances controlled with neutral density filters in the projection path: 0.1, 1, 10 and 100 cd/m^2). Eight conditions were tested, comprising combinations of stationary/dynamic (S/D); positive contrast/negative contrast (+/-), and high contrast (CH = 0.88)/low contrast (CL = 0.1). The dynamic stimulus was an optotype moving in a circle with a diameter of 16° and a velocity of 13°/s.

Results: Low contrast visual acuity (VA) was lower than high contrast VA. There was no difference in VA between positive or negative contrast stimuli. For high contrast stimuli, VA increased with increasing lighting levels and reached a plateau at 10 cd/m^2 for dynamic as well as for stationary conditions. For low contrast stimuli, VA increased with increasing lighting levels up to 10 cd/m^2 and strongly decreased for higher levels. Low contrast VA for dynamic stimuli was lower than for stationary stimuli. Highest VA was reached at a level of 10 cd/m^2. Detecting a moving low contrast object was the most difficult task for the patient.

Conclusions: For this patient, luminance higher than 10 cd/m^2 caused a drop in low contrast VA, with perception of dynamic stimuli being worse than perception of stationary stimuli. These results demonstrate that for a bradyopsia patient, visual functioning in a high luminance environment may become problematic. For example, spotting a moving dark ball against a bright background may be very difficult, which was one of the complaints reported in our patient. Because of the large range of luminance in daily life, we advised the patient to wear a combination of dark tinted neutral density contact lenses with sun glasses and clip-on sunglasses.

9.04 Comparison between mobile ERG with ERG-jet and skin electrode and full-field ERG

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Purpose: To find differences between ERGs in normal subjects measured by a mobile electroretinography system (RETeval, LKC Technologies, Gaithersburg, MD) with ERG-jet electrode (Fabrinal SA, La Chaux-De-Fonds, SZ) and skin electrode, and a conventional ganzfeld system (LKC Technologies, Gaithersburg, MD) with ERG-jet electrode.

Methods: We measured full-field ERGs (six basic responses standardized by ISCEV) with a conventional ganzfeld system and with a mobile system (RETeval) in five normal people (10 eyes). We used ERG-jet electrodes for the conventional ganzfeld system, and ERG-jet electrodes and skin electrodes with the RETeval. We recorded twice with each system. We dilated pupils only for the conventional ganzfeld system. Participants had no general or ophthalmologic history and visual acuity better than 20/25.

Results: Compared to conventional ganzfeld ERGs, mobile RETeval ERGs with ERG-jet electrodes showed no significant differences except for the maximum combined ERG b-wave. Average b-wave amplitude of mobile RETeval ERGs with ERG-jet electrodes (mean 375.3±51.2 μV) was 3.1 times larger than those of conventional ganzfeld ERGs (p=0). When using skin electrodes, amplitudes of all RETeval ERGs were significantly lower than conventional ganzfeld ERGs. Average amplitude of rod-system ERG (mean 27.1±9.0) was 1.8 times smaller; maximum combined a-wave (mean -43.3±7.2) was 4.5 times smaller and b-wave

(mean 63.0±13.5) 1.9 times smaller; OPs (mean 56.1±15.0) were 3.6 times smaller; single flash cone a-wave (mean -6.0±1.6) was 7.8 times smaller and b-wave (mean 16.4±6.1) 3.7 times smaller; and 30 Hz flicker (mean 16.7±5.7) was 4.0 times smaller than conventional ganzfeld ERGs.

Conclusions: Mobile electroretinography is much easier and faster than conventional ganzfield ERG and can be hand-held facilitating examination of infants and immobilized people. However, the mobile RETeval's typical skin electrode is attached to the skin under the eye and it can be disturbed or measured not constantly depending on depth of skin and other variations. We compared mobile electroretinography with conventional ganzfeld ERGs. As we mentioned in the results, there were differences in amplitude between mobile ERGs and conventional ganzfeld ERGs. Therefore, when a mobile electroretinography sys is used, these differences should be considered.

9.05 Retinal toxicity of electroluminescent diode (LED) lighting systems

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Purpose: Electroluminescent diodes (LEDs or solid state lighting) are widely used nowadays, as public or domestic lighting systems, essentially for economic reasons: LEDs are supposed to consume 10 times less energy than incandescent lamps. Consequences on human and animal vision are not part of this political choice. For years, manufacturers claimed absence of retinal toxicity based on lack of retinal whitening. However, we know now that usual toxicity tests are not adapted to LED lighting system, because they detect thermal damage, whereas LED light induces phototoxicity. Indeed, acute rat exposure to white LEDs induces macroscopically eye and conjunctiva redness and face oedema but no whitening of the retina at slit lamp examination.

Methods: We submitted rats to various exposure protocols: an acute exposure to high luminance LEDs for 24 h, or chronic exposure to usual domestic luminance following sequences of 12 h light and 12 h dark for 1 week or 1 month. Three wavelengths were used to compare their retinal toxicity: 473 nm (green LED), 449 nm (blue LED), and white LED. Electroretinography was performed before and after light exposure. Mean changes in ERGs were compared between pigmented and albino rats. The rat retinas were taken for histology and immunohistochemistry analysis. We quantified the thickness of retinal layers and observed immunohistochemical labelling of Nitro-Tyrosine and 8-Hydroxyguanosine (proteins and nucleic acid oxidative stress markers) and glial fibrillary acidic protein (retinal inflammation marker).

Results: Following chronic LED exposure, a-wave and b-wave amplitudes of the scotopic ERG deteriorated in both pigmented and albino animals. The first and second OPs were also altered. The albino rats were more sensitive to light toxicity. Histologic and immunohistochemical studies showed that blue LEDs are more toxic than green ones, which are more toxic than white ones. Exposure to LED light induced protein and nucleic acid damage that was greater when using blue LEDs compared to green LEDs. Both acute and chronic exposure protocols induced photoreceptor degeneration, especially in the superior retina. Pigmented rat retinas were damaged to a lesser extent than the albino rats.

Conclusions: Acute exposure to high LED luminance induces retinal phototoxicity, as assessed through inflammation, oxidative stress, photoreceptor death, and reduction of the ERG. Chronic exposure to usual luminance induces less histological damage, but alteration of the ERG is an indicator of early retinal damage in those conditions. Both pigmented and albino rat retinas are sensitive to LED exposure; however, pigmented rats are less protected against LED light than against other types of lighting systems. Caution should be taken since no experiment reproduces chronic exposition during a lifetime. Present phototoxicity norms are not adapted to LED lighting systems. The French food, environment and work safety agency (ANSES) should publish soon a new report with updated recommendations.

9.06 Fractal optical stimulation improves visual field indices in glaucoma patients

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Purpose: To assess the impact on sensitivity in the visual field (VF) of low-intensity fractal photo-stimulation therapy in eyes with suspected glaucoma (SG) and eyes with primary open-angle glaucoma (POAG).

Methods: The study included 39 patients with SG (50 eyes) and 58 patients (80 eyes) with POAG of State I (50 eyes), Stage II (13 eyes), and Stage III (17 eyes). Mean age was 58 (range 40-72). Normal control values were collected from 50 healthy individuals (50 eyes) without eye pathology, mean age 48 (range 35-56) years. Standard automated perimetry (SAP; Humphrey, Carl Zeiss Meditec, Ltd.) was performed with the 30-2 threshold test program using the SITA-Standard algorithm. The dynamics of the perimetric indices mean deviation (MD) and pattern standard deviation (PSD) were evaluated before and after a course of 10 sessions of photo-stimulation (10 minutes daily, except on weekends) with the permission of the Local Ethical Committee of the Voronezh State Medical University and with the informed consent of the patients. Low-intensity fractal stimulation was performed using an LED emitter mounted in the body of virtual reality glasses. Stimulator formed complex-structured optical signals (10–12 Lx at the cornea) with a given fractal dimension.

Results: The SITA-Standard perimetry revealed depression in the VF sensitivity, the depth of which depended on the stage of glaucoma. The normal MD values should not exceed −2 dB. Before fractal stimulation phototherapy, in the SG group, MD = -2.55±0.7 dB and the PSD = 2.46±1.15 dB. After treatment, the MD and PSD values were -1.55±0.6 dB and 2.34±1.3 dB, respectively. In the POAG-I eyes, the MD and PSD indices were, respectively, -5.13±1.3dB and 2.58±0.9dB before the fractal phototherapy course and -4.36±1.2 dB and 2.27±0.79 dB after. The MD values for POAG-II and POAG-III, respectively, before the treatment were on average -3.42±0.65 dB and -14.37±1.05 dB; after phototherapy, they decreased up to -1.75±0.7dB and -9.98±0.9dB, respectively. The PSD values for POAG-II and POAG-III before/after phototherapy, respectively, were -1.99±0.85 dB/-1.89±0.9 dB and -6.58±0.85/-6.28±0.95 dB. Surprisingly, the opposite effect was found in several eyes with POAG-II and POAG-III where the VF defect decreased by 0.67 to -4.39 dB.

Conclusions: In this study, we first used the fractal stimulation technology developed by us for glaucoma therapy and showed a positive effect both at the stage of SG and in early and advanced glaucoma. The 2-week, low-intensive, fractal stimulation phototherapy significantly improved the MD indices, which estimate the average defect in the VFs, in all the groups. The obvious effect of fractal stimulation for the advanced POAG can indicate that at any stage of glaucoma, in the general population of ganglion cells there is a significant percentage of cells that are yet at the plastic phase of reversible functional changes and capable of responding positively to medicinal or physical neuroprotective therapy. Further confirmation of the magnitude and stability of effects is required in studies on a more massive cohort and using an objective examination such as the ERG, VEP, and EEG analysis.

9.07 Retinal sites and function affected by hydroxychloroquine therapy

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Purpose: To investigate the effects of hydroxychloroquine (HCQ) on retinal sites and function in patients.

Methods: Thirty five eyes of 35 patients (10 -78 years) on HCQ therapy were included in this cross-sectional study. Each patient had a complete ophthalmologic examination and the following recommended screening tests: 10-2 visual fields; spectral domain ocular coherence tomography

(SD-OCT) volume scans (Spectralis Heidelberg Eng.); fundus autofluorescence (FAF), and mfERGs. For the mfERG, the 103-hexagon P1 amplitude response densities were analyzed by averaging the 103 responses into six concentric rings and calculating ring ratios using the R5 ring response as the "reference ring" and dividing by all other ring response amplitudes (R1 - R6) (Lyons J.S., Severns M.L. *Am J Ophthalmol*. 2007;143:801-809; Adam M.K. et al. *BJO* 2012; 96:723-9). The ratios of R5 to each of the other rings were compared to 95% CIs from control eyes.

Results: Of the 35 patients, 7 had been treated with HCQ for <5yrs and 28 for >5 yrs. Twenty one of the 28 patients had a cumulative dose >1000g and 16 had a daily dosage >5.0mg/kg of real body weight. Twelve of the 28 patients had either partial (superior field) or complete ring scotomas and/or mfERG abnormalities affecting the central 5-10°. Seven of these patients had outer retinal abnormalities on OCT ranging from disruption of the EZ and IZ band in the parafovea, thinning of the ONL, to atrophy of the RPE in the central macular area. For five patients, these structural deficits appeared to be more pronounced in the inferior macular region.

Conclusions: In agreement with previous reports (Greenstein V.C. et al. *Doc Ophthalmol*. 2015;130:20-33; Marmor M.F., Melles R.B. *Ophthalmol.* 2014;121:1257-62), we found disparities between the results of functional and structural measures. Five of the 12 patients had visual field and/or mfERG deficits that were not accompanied by OCT or FAF abnormalities. As mfERG deficits reflect damage at or before the level of the bipolar cells, this suggests that there are changes affecting the outer retina at the cellular level that cannot be detected with current OCT technology. In addition, the finding that visual field deficits tended to be more pronounced in the superior field and structural deficits on OCT in the inferior macular region suggests that this retinal region is more susceptible to toxicity.

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9.08 ERG changes in Dp71-knock out mice

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Purpose: Müller cells are the main type of glial cells in the retina. Amongst other functions, they are responsible for the extracellular ionic balance. Dp71, a short product of the dmd gene, is expressed by Müller cells. It is associated with a protein complex responsible for the proper distribution of membrane channels, such as AQP4 and Kir4.1, which allow extracellular water and ionic balance in the retina. It has not been clearly established if deletion of Dp71 alters the electrophysiology of the retina. The purpose of the present study is to investigate the electrophysiological changes in Dp71-knock out mice.

Methods: We recorded binocular full-field ERGs from 18 Dp71-knock out mice (Dp71ko; mean age 85.3 ± 7.0 days) and from 12 wild type littermates (WT; mean age 76.2±8.0 days). Animals were anaesthetized by an intramuscular injection of 25:5 mg/kg ketamine:xylazine. Experiments were approved by the Institutional Ethics Committee. ERGs were measured to the following stimulus conditions: 1) flashes (strengths from -3.7 to 0.3 log cd s/m²) during dark adaptation (scotopic flashes); 2) rapid-on and rapid-off sawtooth stimuli at 1 cd/m² mean luminance (mesopic on- and off-responses); 3) 0.3 log cd s/m² flashes on a 30 cd/m² background (photopic flashes); 4) sinusoidal luminance modulation (100% contrast; 60 cd/m² mean luminance) at 10 temporal frequencies from 3 to 30 Hz (photopic flicker); and 5) rapid-on and rapid-off sawtooth stimuli at 60 cd/m² mean luminance (photopic on- and off-responses). Stimuli were provided by a ganzfeld bowl (Q450SC) and signals were registered using the RetiPort system (Roland Consult, Brandenburg, Germany).

Results: 1) Scotopic flashes: significantly smaller b-wave amplitudes (Dp71ko 373±167 µV, WT 480±172 µV; $p<0.05$) in Dp71ko mice compared to WT with no alterations in a-wave amplitudes, implicit times of a- and b-waves, or OPs. 2) Mesopic on- or off-responses: no differences. 3) Photopic flashes: reduced b-wave amplitudes (Dp71ko 81±31 µV, WT 123±44 µV, $p<0.05$). 4) Photopic flicker: reduced amplitudes of the first harmonic (fundamental) response components to frequencies between 3 and 12 Hz. 5) Photopic on- and off-responses: reduced amplitudes of the on-response.

Conclusions: We demonstrate that a selective loss of Dp71 reduces the amplitude of the b-wave, as found in mdx3cv mice lacking all dystrophins (Tsai T.I. et al. *Invest Ophthalmol Vis Sci* 2016;57:5788–98), nonetheless without affecting the implicit time. We suggest that the deletion of Dp71 in Müller glial cells causes an ionic extracellular imbalance in the retina, due to the mislocalization of AQP4 and/or Kir4.1, leading to a reduction of the b-waves in both scotopic and photopic ERGs in mice. Recently it has been reported that Dp71 can be restored after adeno-associated virus (AAV) transfection (Vacca O. et al. *Hum Mol Gen* 2016;25:3070–79). The present data form a basis to study functional recovery after Dp71 restoration.

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9.09 Multiple evanescent white dot syndrome (MEWDS): electrophysiological evidence of retinal ganglion cell dysfunction

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Purpose: Multiple evanescent white dot syndrome (MEWDS), first described in 1984, is characterized by the appearance of altered visual fields, often with increased blind spot or paracentral scotoma, decreased visual acuity (VA), photopsias and myodesopsias, being more frequent in young female patients, from 15 to 50 years. It typically affects only one eye and has spontaneous resolution in 4 to 6 weeks. OCT demonstrated the reduction of the retinal ganglion cell layer, which was maintained after complete resolution of symptoms and a complete recovery of the ellipsoid (Hakayama H. et al. *BMC Ophthalmol* 2014;14:132). However, functional evaluation of retinal ganglion cells has not been described so far in patients with MEWDS.

Methods: We performed clinical and electrophysiological evaluation of a 17 year old patient with MEWDS in the initial phase of the disease and 6 weeks after the onset of symptoms, with fluorescein angiography (FA), indocyanine green angiography, ocular coherence tomography (OCT), autofluorescence, Goldman kinetic perimetry, and electrophysiological evaluation with flash ERG, PERG, mfERG, and pattern VEP.

Results: The patient had decreased VA and paracentral scotoma in the right eye, observed four days after the onset of symptoms. The presence of multiple whitish spots in the peri-macular region and foveal granularity was evident. FA showed multiple clusters of hyperfluorescence early on and later showed impregnation of the optic disc. Indocyanin green angiography showed multiple hypofluorescent points. OCT showed the ellipsoid to be disrupted. An increase in the blind spot was evident in Goldmann kinetic perimetry. Based on these findings, the diagnosis of MEWDS was made. Electrophysiological evaluation showed no changes in the flash ERG or in the pattern VEP. In the mfERG, a decrease in the central response (R1) was evident, with the remaining rings within normal range. In the PERG, the N95 wave was decreased, with a normal P50 wave, compatible with retinal ganglion cell dysfunction. The clinical and electrophysiological evaluation was repeated 6 weeks after the onset of symptoms. At that time, FA, indocyanine green angiography and OCT were normal. An increase of the blind spot was present, although smaller than initially. The electrophysiological evaluation was normal, with full reversal of PERG and mfERG changes.

Conclusions: This is the first report in the literature of the PERG and evaluation of retinal ganglion cell function in patients with MEWDS. The reduction in

the N95 wave observed in the PERG performed 5 days after the onset of symptoms suggests retinal ganglion cell dysfunction. The decrease in the retinal ganglion cell layer described in 2014 by Hakayama et al. appears to have a functional repercussion. However, unlike the structural change that is maintained over time, the function of retinal ganglion cells seems to recover after 6 weeks.

9.10 Ocular features in Chinese patients with Blau syndrome

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Purpose: Blau syndrome (BS) is a rare familial granulomatous disease transmitted as an autosomal dominant trait, featuring skin rash, fever, chronic arthritis and recurrent uveitis. The purpose of this study was to identify pathogenic gene variants and to assess the clinical features of a cohort of Chinese patients affected with BS.

Methods: Detailed ophthalmological examinations were performed on eight patients from seven unrelated BS families, including best corrected visual acuity (BCVA), intraocular pressure, slit-lamp biomicroscopy, dilated indirect ophthalmoscopy, B scan ophthalmic ultrasound, visual field, and ocular coherence tomography (OCT). Genomic DNA was extracted from peripheral blood. Sanger sequencing was used to analyze NOD2 gene.

Results: A total of eight patients, five males and three females, were recruited for this study. Six were school children and two were adults (median age 10.5 years, range 4–34 years). Positive family history occurred in two families. The onset of ocular manifestations was different (median age 5.5 years, range 2–24 years). BCVA (decimal) ranged from LP to 1.0, with seven eyes worse than or equal to 0.3, six eyes better than 0.3 and worse than or equal to 0.6, and three eyes better than 0.6. The systemic manifestations included fever, lymphadenopathy, abnormal liver and renal function, hypertension, hypercalcemia, atrial enlargement, and pericardial effusion. Two patients presented with recurrent anterior uveitis, five had panuveitis, and one was at phthisis bulbi stage. Band keratopathy was found in all patients. Vitreous opacities, optic disc edema, and macular edema were observed in patients with panuveitis. One novel disease associated variant (c.2006A>G, p.His669Arg) and four reported disease associated variants (c.1000C>T, p. Arg334Trp; c.1001G>A, p. Arg334Gln; c.1442G>A, p.Gly481Asp; c.1759C>T, p.Arg587Cys) in NOD2 gene (NM_022162.1) were identified.

Conclusions: Blau syndrome is a rare autosomal dominant multi-system disease caused by NOD2 gene defect. Recurrent anterior or panuveitis is the characteristic ocular sign, which is usually complicated with secondary glaucoma and band keratopathy. Visual function was markedly reduced when the posterior segment was involved. The severity of vision loss was also related to the duration of the oculopathy. Early detection and treatment of ocular disease are crucial to preserve vision.

9.11 Distribution of generalized functional phenotype of East Asian patients with Stargardt disease (STGD1): EAStar studies report 2

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Purpose: To describe functional phenotypic features of East Asian patients with Stargardt disease (STGD1).

Methods: Patients with a clinical diagnosis of STGD1 caused by ABCA4 pathogenic variants were enrolled in Japan, South Korea, and China. Patients were classified into the previously established three generalized functional phenotypes based on the findings of full-field ERGs: Group 1 (n=18) - dysfunction confined to the macula; Group 2 (n=4) - macular and generalised cone system dysfunction and Group 3 (n=14) - macular and generalised cone and rod system dysfunction. To characterize the functional phenotypes, statistical analysis was performed between groups in terms of clinical parameters; age of onset, duration of disease, and logMAR visual acuity (logMAR VA). One eye was randomly selected for statistical analysis of logMAR VA.

Results: Thirty six patients with available full-field ERG data were recruited. The median age/age of onset were 28.0/12.5 years (range 14.0-85.0/6.0-70.0), with the median duration of disease of 12.5 years (range 2.0-45.0). The median logMAR VA was 1.1 (range 0.22-2.28). The median age/age of onset in groups 1, 2 and 3 were 26.5/13.0 years (range 14.0-46.0/8.0-31.0), 40.5/11.0 (range 28.0-58.0/11.0-33.0), and 36.5/11.0 (range 18.0-85.0/6.0-70.0), respectively. The median duration of disease in groups 1, 2 and 3 were 13.0, 17.5, and 15.0 years (ranges 8.0-31.0, 11.0-33.0, 2.0-45.0), respectively. The median logMAR VA for the selected eyes for groups 1, 2 and 3 were 0.91, 0.82, and 1.55 (ranges 0.0-1.3, 0.82-1.7, 1.1-2.28), respectively. There was a statistically significant difference in logMAR VA between groups 1 and 3. No significant differences were observed in onset, age, or duration.

Conclusions: Distribution of generalized functional phenotype was documented in the East Asian cohort with STGD1. Severe visual impairment was observed in patients with generalized cone and rod dysfunction, which is in keeping with the previous studies of the Caucasian population. Further studies of a larger cohort will help in delineation of the characteristic functional features of East Asian STGD1.

9.12 Bull's eye maculopathy with negative ERGs in retinal dystrophy

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Purpose: Bull's eye maculopathy is thought to be caused by malfunction of the retinal pigment epithelium. It may be accompanied by a negative ERG in several retinal pathologies, both acquired and congenital. It is rare that the two phenotypes occur together in inherited cases. The aim of this study was to examine phenotypes and genotypes underlying the finding of bull's eye maculopathy with negative ERGs in a cohort of patients with this condition.

Methods: The results of six patients with bull's eye maculopathy and a negative ERG in the dark-adapted bright-flash ERG recording were analysed retrospectively. They were aged between 11 and 63 years, three males and three females, and had all undergone a complete ophthalmological examination including visual acuity determination, fundus photography, ERG, and genetic analysis. Most patients also underwent ocular coherence tomography (OCT) imaging, fundus autofluoresence (FAF), kinetic visual field determination, and colour vision testing with either the saturated or desaturated D-15 panel.

Results: Two of the six patients, who were diagnosed with cone-rod dystrophy, were shown to have mutations in either the CRX or PDE6C genes. One patient was diagnosed with cone dystrophy and had a mutation in GUCY2D, one patient had fundus flavimaculatus with ABCA4 mutation, and two patients with retinitis pigmentosa had mutations in CLN3 and HGSNAT. Patients with mutations in the genes CLN3, PDE6C, HGSNAT showed reduced a-waves and reduced b-waves in the ERG recording, whereas patients with mutations in the genes GUCY2D, ABCA4 and CRX showed only a reduced b-wave with a normal a-wave.

Conclusions: The group of six patients with bull's eye maculopathy marked by a negative ERG were heterogeneous in their genotype, with each patient carrying a mutation in different genes. We identify to date unpublished mutations that are involved in this phenotype. Whereas ERG b-wave reduction may indicate bipolar involvement in the visual deficit, additional factors may lead to a-wave reduction.

9.13 Autosomal recessive bestrophinopathy: a case series

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Purpose: Autosomal recessive bestrophinopathy (ARB) is a recently described clinical entity which is consecutive to the presence of two mutations in BEST1 gene. The presentation is uneven and the diagnosis may be difficult in children. Electrophysiology allows elimination of differential diagnoses and support of the clinical presumption.

Methods: We performed a retrospective observational study of cases diagnosed as ARB. Patients were examined in the ophthalmology department of Necker-Enfants Malades University Hospital. Multimodal imaging had been performed for each patient. Full-field ERG and sensory EOG helped the diagnosis of ARB, which was confirmed with a molecular study.

Results: Four patients presented with ARB, two adults and two children. No anomaly was identified in the parents of the two children. Patients presented with acuity ranging from "counting fingers" to 1.0 (decimal). Lesions were associated with macular yellowish deposit of material at the posterior pole, patchy atrophy areas, or pigmented lesions. On spectral domain ocular coherence tomography (SD-OCT), a pathological triad was noticed: hyperreflective subretinal material, subretinal fluid, and macular schisis. In all cases, the full-field ERG was normal but the EOG showed a severely reduced Arden ratio, eliminating retinal dystrophies or enhanced s-cone syndrome, which are the main differential diagnoses. There was no correlation between clinical presentation and ERG or EOG results. Electrophysiology alone could not differentiate between typical Best macular disease and these four cases of ARB, but the clinical presentation was unmistakable. For each patient, two mutations were identified in BEST1 gene.

Conclusions: We present the ophthalmological features of a series of four patients with ARB. A normal ERG associated with an impaired EOG confirmed the clinical diagnosis. Molecular analysis with two mutations in BEST1 gene enabled a formal diagnosis. The visual prognosis of ARB is very variable, from normal central acuity to low vision due to various retinal complications.

9.14 Intravitreal injection of bevacizumab in case of syphilitic retinitis with retinal neovascularization

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Purpose: To report a case of syphilitic retinitis with retinal neovascularization (NV) treated with an intravitreal injection of bevacizumab (IVB) combined with conventional therapy.

Methods: A 29 year old man had experienced night blindness and a gradual reduction of vision for a year. An earlier examination in a neighboring

eye clinic showed chorioretinal atrophy with pigmentary changes resembling retinitis pigmentosa. Humphrey visual field examinations (HFA 30-2) showed retinal sensitivity decrease OU.

Results: At the first visit, the patient's best corrected visual acuity (BCVA) was 20/20 OU. The critical flicker frequency (CFF) was 43.7 Hz OD and 40.2 Hz OS. Slit-lamp examination revealed no inflammation in the anterior chamber or vitreous OU. Fundus examination showed chorioretinal atrophy with pigmentary changes and NV around the reddish optic discs. A shortening of the ellipsoid zone was detected by ocular coherence tomography (OCT) imaging. The b-waves of the scotopic ERGs were reduced and the implicit times were prolonged. Fluorescein angiography revealed staining and dye leakage around the optic disc OU. HFA 30-2 visual fields showed a decrease in retinal sensitivity OU. Laboratory examinations showed a positive Treponema (TP) antibody, high rapid plasma reagin (RPR) test (1:512), and a Treponema pallidum (TPHA) hemagglutination assay of 1:40960. HIV was negative. The patient was diagnosed with syphilitic retinitis and was treated with daily doses of 6 g oral amoxicillin for 4 weeks and IVB for the retinal NV. Also, oral administration of prednisolone was required to prevent the intraocular inflammation induced as Jarisch-Herxheimer reactions. After the treatment, the RPR was markedly reduced to 1:64 and the TPHA was reduced to 1:10240. His BCVA remained 20/20 OU. Fundus examination showed no NV around the optic discs. Fluorescein angiography revealed no leakage around the optic disc OD and decreased leakage around the optic disc OS. HFA 30-2 showed improvement of retinal sensitivity OU but the ERGs and OCT were unchanged.

Conclusions: The findings in this case of syphilitic retinitis with retinal NV around the discs showed that IVB was effective in decreasing the activity of the NV.

9.15 Using Diagnosys full-field stimulus threshold testing (D-FST) to quantify scotopic thresholds in patients with proliferative and non-proliferative diabetic retinopathy

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Purpose: Studies using dark adaptometry methods in diabetic retinopathy (DR) patients demonstrate reduced photoreceptor function, including deficits in the rods and cones with worsening function as DR progresses from non-proliferative diabetic retinopathy (NPDR) to proliferative diabetic retinopathy (PDR) (Bavinger J.C. et al. *Invest Ophthalmol Vis Sci* 2016;57:208-17). The Diagnosys full-field stimulus threshold test (D-FST) has been established as a psychophysical indicator of dark-adapted deficits in low vision individuals (Roman A.J. et al. *Exp Eye Re*s 2005;80:259-2; Klein M., Birch D.G., *Doc Ophthalmol* 2009;199:217-24). It has been demonstrated that D-FST tests an individual's detection abilities in sensitive parts of the retina, and the use of white, red and blue light allows for quantification of rod and cone thresholds. The purpose of this study was to determine whether D-FST can detect scotopic threshold differences in patients with NPDR and PDR.

Methods: In this prospective study, individuals in the DR patient population were evaluated for functional photoreceptor deficits using D-FST. The cohort included 35 eyes of 28 NPDR patients and 13 eyes of 12 PDR patients. There were 11 mild patients, 10 moderate patients, and 13 severe patients for the NPDR subgroup. The diagnosis was confirmed with Hb1Ac measurements, and a full eye exam with best-corrected visual acuity (BCVA) testing was performed before dark adaptation. Each patient was also graded on the Early Treatment of Diabetic Retinopathy Study (ETDRS) scale. After 25 minutes of dark adaptation, the Espion E2 system with the ColorDome LED full-field stimulator (Diagnosys LLC, Lowell, MA, USA) was used to perform three trials for each color per eye. Patients were tested in the following sequence of stimuli (with accompanying wavelengths): red (635-638 nm), blue (465-470 nm), white (6500 K). An ANOVA with a Bonferroni multiple comparison test was used to identify significant differences between the groups. A p-value <0.05 was considered statistically significant.

Results: For the NPDR group, the mean (SD) age was 56.86 (9.76) years, 50% were males, and the median BCVA was 0.30 (6/12). For the PDR group, the mean (SD) age was 51.83 (6.21) years, 22% were males, and the median BCVA was 0.30 (6/12). In the NPDR group, the mean (SD) threshold was

-31.42 (4.37) for red, -45.79 (4.08) for white, and -50.18 (5.18) for blue. In the PDR group, mean (SD) thresholds were similarly -31.50 (3.37) for red, -44.96 (4.47) for white, and -50.79 (4.61) for blue. There were no statistically significant differences between the NPDR and PDR groups ($p>0.999$) for red, white, or blue thresholds. When comparing mild, moderate, and severe NPDR patients, there were also no significant differences between red, white and blue thresholds ($p>0.05$).

Conclusions: We had hypothesized that photoreceptor dysfunction, as measured by D-FST, would increase with severity of DR, as was previously shown by other dark adaptometry methods. Our results, however, suggest that scotopic thresholds determined by D-FST do not significantly differ between PDR and NPDR groups in this patient population.

9.16 Exploratory clinical trial to examine the safety and efficacy of transdermal electrical stimulation for patients with retinitis pigmentosa

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Purpose: This exploratory clinical trial was performed to verify the safety and efficacy of transdermal electrical stimulation (TES) with skin electrodes for patients with retinitis pigmentosa and to evaluate visual function before and after treatment.

Methods: This is single arm, non-randomized, open-label uncontrolled study. Twenty eyes of 10 patients (mean age 53.3±7.4; six males) with typical retinitis pigmentosa without any other ocular abnormalities were studied. Patients underwent TES (10 ms biphasic pulses, 20 Hz, 30 minutes) using the prototype equipment jointly developed with Mayo Co., Ltd. Electrodes were applied to the skin at the center of the forehead of the patient and on the eyelid's ear side of both eyes. All patients were stimulated in both eyes with 1.0 mA simultaneously in the hospital by physicians. The primary endpoint was safety; secondary endpoints were efficacy measurements via visual acuity (VA), visual field, intraocular pressure, ocular coherence tomography (OCT), and visual function questionnaire-25. Electrical stimulation was performed six times every 2 weeks, and patients were examined at the baseline, before treatment, 1 hour after treatment end, and 2 weeks after treatment.

Results: All patients completed the study per protocol. No serious adverse events (AEs) related to the treatment were reported during the follow up examinations. The mean logMAR VA was 0.35±0.17 before TES and 0.29±0.16 after TES. The mean ETDRS visual acuity was 31.7 letters before TES and 35.4 letters after TES. Mean deviation and average value of the sensitivities of the central four points of Humphrey field analyzer (HFA) 10-2 were -21.35 dB and 21.25 before TES and -22.19 dB and 22.31 after TES. The mean area of visual field defined by the Ⅰ/4 white test light with the Goldmann perimeter was 2820 pixels before TES and 3335 pixels after TES. There were no significant differences in the examination results before and after TES in the comparison between right eyes and left eyes.

Conclusions: AEs due to TES were not observed and there were cases in which improvement of visual function was observed by TES. Although the present study tested only a small number of patients, our result suggests that TES with skin electrodes may be a safe therapy for patients with retinitis pigmentosa.

9.17 Full-field dark-adaptation and full-field ERGs over 2 year follow-up in patients with RLBP1 retinitis pigmentosa enrolled in a prospective natural history study

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Purpose: Retinitis pigmentosa (RP) due to biallelic mutations in the RLBP1 gene (RLBP1 RP) is an autosomal recessive form of RP, with a hallmark of severely delayed dark adaptation. A prospective natural history study was initiated to evaluate functional and structural endpoints in RLBP1 RP patients. Here, we report preliminary 2 year results on the variability and progression of measures of visual function.

Methods: This was a non-interventional, two center (Sweden and Canada), prospective study. Forty-five RLBP1 RP patients were enrolled in the study; patients were evaluated every six months. Among other measures, full-field dark-adaptation parameters were measured (Diagnosys LLC) in one eye at 450 and 632 nm wavelengths for 6 hours after overnight dark adaptation. Post-dilation, three threshold measurements were obtained at multiple time points pre-bleach and post-bleach up to 6 hours. The median of three repeated threshold measurements was used for the kinetic curve. A subset of patients (n=15, Canada) had ISCEV standard, full-field, light-adapted 30 Hz flicker ERGs with ganzfeld stimulation (following pupil dilation). Annual progression (slope) was estimated using a random effect linear growth model and test-retest repeatability was assessed using the intra-class correlation coefficient (ICC) and Bland-Altman plots. Pearson's correlation coefficients and scatter plots were used to describe correlation among measures. Between-eye correlations were estimated for each measurement at each visit.

Results: There was high test-retest repeatability across the end points; however, the repeatability of the ERG was lower than for other measures (but with fewer observations). All the measures also showed significant between-eye correlations over the course of the study. The RLBP1 RP patients showed severe delays in dark adaptation at both wavelengths with recovery to pre-bleach levels after 3 to 6 hours. Additionally, patients had abnormal dark adaptation final thresholds which correlated significantly with age and best-corrected visual acuity (BCVA) at baseline. The RLBP1 patients had reduced or non-measurable full-field ERG amplitudes with delayed implicit times. The ERG measures correlated significantly with other measures of visual function, including Humphrey threshold visual field mean deviation. There was no significant disease progression measured by dark-adaptation thresholds or full-field ERG parameters over the first 2 years of follow-up in this study.

Conclusions: RLBP1 RP patients showed severely delayed dark adaptation that was dependent on their age and level of visual function. There were flicker ERG deficits present in the group of patients examined that are consistent with photoreceptor degeneration. The two eyes show similar effects, as shown by the high correlations between the right and left eyes. Despite large individual differences between patients on the dark adaptation and ERG measures, there was a high degree of within-measure repeatability across the visits. For these measures, there was no statistically significant progression over the 2 year follow-up.

9.18 PDE6B mutation presenting with retinitis pigmentosa: a report on three patients

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Purpose: Retinitis pigmentosa (RP) occurs with an incidence of 1:3500, affecting 2.5 million worldwide. In the last 20 years, causative gene defects have been increasingly identified and targeted gene therapy has become possible in some cases. In addition to understanding the phenotype, genotype correlations are important in order to help identify patients who would benefit from targeted gene therapy and to improve patients' care. Here we report on three RP patients with mutations in the PDE6B gene that have not been described previously.

Methods: Patients: Three patients with a PDE6B mutation were identified: (1) a 30 year old male with a homozygotous mutation (c.[2351dupA], p.[Q785Gfs*20]) who was followed for eight years; (2) a 54 year old Caucasian woman with a heterozygous mutation (p.(K611Nfs*6) , p.(Q567*)) who was followed for 40 years; (3) a 46 year old Caucasian male (p.(E271K), p.(R627_E631del)).

Results: All three patients had noted an onset in childhood and complained of night blindness and photophobia. Typical bone spiculae were seen in all three patients and peripheral visual fields were progressively affected in all patients. Ganzfeld ERGs showed typical signs of rod-cone dystrophy. Patients 1 and 2 underwent cataract surgery at age 27 and 36 years, respectively, with improvement in vision; patient 3 had not developed a cataract at age 43.

Conclusions: In children complaining of night blindness, a PDE6B-associated RP needs to be taken into consideration. Apart from helping patients with optical aids such as polarizing filters or magnification, specific diagnosis is especially important in view of emerging genetic treatment options, in particular in RP patients with a PDE6B mutation. A phase II/III study is currently ongoing (ClinicalTrials.gov identifier: NCT03328130).

9.19 Correlations between mfERG and OCT angiography

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Purpose: To assess morphological and functional macular changes in subjects with normal and abnormal fundus using ocular coherence tomography angiography (OCT-A) and mfERGs.

Methods: OCT-A and mfERG recording were performed on eight healthy controls (11 eyes) and 13 patients (20 eyes). Patient characteristics included diabetic retinopathy, age-related macular degeneration, epiretinal membrane, branched retinal vein occlusion, staphyloma, and fundus albipunctatus. Foveal avascular zone (FAZ) size, vessel density (VD), perfusion of superficial capillary plexus (SPC) on OCT-A, and amplitude and implicit time of mfERG ring 1 were analyzed.

Results: The FAZ size was 0.23 mm^2 in normal controls and 0.26 mm^2 in patients. VD was 8.4 mm^{-1} in normal controls and 7 mm^{-1} in patients with abnormal fundi. N1, P1, and N2 (ring 1) amplitudes were reduced significantly in the eyes with abnormal fundi compared to the normal controls ($p<0.05$). There were correlations between central VD, perfusion of SPC, horizontal diameter of FAZ, and mfERG ring 1 N1, P1, and N2 amplitude and N2 implicit time ($p<0.05$).

Conclusions: FAZ size was increased and VD was decreased in eyes with abnormal fundi compared with normal controls. mfERG responses were decreased in patients with abnormal fundi. These results suggest that OCT-A and mfERG are useful tools to investigate the morphology and function of the fundus in patients with abnormal fundus.

9.20 Genotype-phenotype association in East Asian patients with occult macular dystrophy (Miyake's disease); EAOMD Report No.4

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Purpose: Two hot spots in the RP1L1 gene including amino acid numbers 45 and 1196-1201 have been recently identified in occult macular dystrophy (OMD). Here, we describe the differential clinical effects of these two hotspots.

Methods: Thirty-six participants from 21 families with OMD caused by pathogenic RP1L1 variants (i.e. Miyake's disease) were enrolled in Japan, South Korea, and China. Patients were classified into two genotype groups: patients with p.R45W variant (Group A, n=20) and patients with missense variants located between amino acid 1196 and 1201 (Group B, n=16). Clinical parameters were statistically compared between these two genotype groups, including age of symptom onset, age at examination and logMAR visual acuity (logMAR VA) of one randomly selected eye. The morphological features obtained with spectral domain ocular coherence tomography (SD-OCT) were also investigated.

Results: The median age of onset/examination was 14.0/34.5 years (range 2-73/11-73) and 43.5/53.0 years (range, 13-63/30-86) in Groups A and B, respectively (p=0.0012). The median duration of disease was 9.0 years (range 0-36) and 11.0 years (range 0-36) in Groups A and B respectively (p=0.9108). The median logMAR VA in the right/left eye of Groups A and B was 0.82/0.70 (range -0.08-1.22/-0.08-1.1) and 0.41/0.56 (range -0.08-1.0/-0.08-0.82) respectively (p=0.0189). The classical photoreceptor findings showing both blurred ellipsoid zone (EZ) and absence of interdigitation zone (IZ) was identified in 17 (17/20, 85.0%) and 13 (13/16, 81.3%) patients in Groups A and B; subtle/early photoreceptor changes of local IZ loss and relatively preserved EZ were found in 3 (3/20, 15.0%) and 3 (3/16, 18.8%) in Groups A and B respectively (p=0.7642). Comparison analyses revealed statistically significant differences in terms of age of onset, age at the latest examination and logMAR VA. There were no significant differences with regards to the duration of the disease.

Conclusions: Different clinical severity derived from the two RP1L1 hotspots were identified; the more severe phenotype of early onset and poor VA was related with p.R45W compared to 1196-1201. This genotype-phenotype association can be helpful for genetic counselling of patients regarding the severity of visual impairment.

9.21 A family with a spectrum of occult macular dystrophy possibly caused by a novel RP1L1 mutation (S1207F)

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Purpose: Mutations of RP1L1 gene were previously reported to be causative of hereditary occult macular dystrophy (OMD; also known as Miyake's disease) and cone dystrophy. However, it was also reported that while the small number of specific variants located at hot spots of RP1L1 gene were pathogenic, a huge number of other variants were not pathogenic. Therefore, it is important to determine the pathogenic variants of RP1L1 gene by the segregation analysis of human family. This study tested the hypothesis that a spectrum of Miyake's disease in a Japanese family was caused by a novel and a rare RP1L1 variant located at a hot spot.

Methods: A family including two affected subjects (daughter II-1, 9 years old and son II-2, 7years old) and two unaffected members (I-1 and I-2, parents of II-1 and II-2) without evidence of consanguinity underwent detailed ophthalmic evaluations including high-resolution imaging of photoreceptor morphology by adaptive optics (AO) fundus photography. Whole exome sequencing, direct sequencing, and in silico molecular analysis were performed for the detection of the pathogenic variants.

Results: Ocular coherence tomography (OCT) images showed the blurring of photoreceptor ellipsoid zone (EZ) and absence of interdigitation zone (IZ) in affected subjects (II-1 and II-2). The father (I-1) showed normal EZ and IZ. The mother (I-2) showed drusen-like RPE abnormality. An affected subject (II-1) had a mildly reduced amplitude of cone and flicker full-field ERGs. AO analysis revealed severely reduced cone density in one of the affected subjects (II-1). Exome sequencing revealed a heterozygous RP1L1 mutation (c.3620C>T, p.S1207F) in both affected subjects (II-1 and II-2) and their father (I-1). The variant was very rare in Japanese and other populations with allele frequency of 0 in both the Human Gene Mutation Database (HMDB, Japanese specific) and the Exome Aggregation Consortium (ExAC) database. The variant was predicted to be damaging by both PolyPhen-2 (HDIV) and SIFT prediction program. The variant was located downstream of the doublecortin domain known as a hot spot of pathogenic RP1L1 variants.

Conclusions: Although the RP1L1 variant S1207F was not perfectly co-segregated with phenotype in the family, in silico molecular genetic evaluations and phenotype in affected members simulating Miyake's disease may indicate the pathogenicity of the variant. Since there are some previous reports of individuals who possess pathogenic RP1L1 variant (R45W) without any abnormality in the retina, incomplete penetrance may play a role in the inheritance of RP1L1.

9.22 Cone dysfunction with normal fundus in two asthmatic patients

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Purpose: To describe progressive visual acuity (VA) loss and cone dysfunction with mfERG in two asthmatic patients. Surprisingly, one patient treated for asthma with mepolizumab (anti-IL-5) showed recovery of cone function.

Methods: A full medical history was obtained and comprehensive ophthalmologic examinations were performed, including ISCEV standard full-field ERG (ffERG) and multifocal ERG (mfERG).

Results: A 54 year old male (Case 1) and a 46 year old female (Case 2) were examined. Case 1 had asthma and eosinophilia. Case 2 had severe asthma. Case 1 noticed VA loss 10 years ago, and his VA was 0.6 in both eyes. Three years ago, Case 2 noticed severe photophobia and photopsia in both eyes; her VA was 0.7 in the right eye and 0.6 in the left eye. VA loss has progressed gradually in both cases, but ophthalmoscopy and ocular coherence tomography (OCT) images did not show any abnormalities. In both cases, ffERGs were almost normal in both eyes. However, mfERGs demonstrated grossly reduced responses in both eyes. In Case 2, her physician started mepolizumab (anti-IL-5) therapy for severe asthma. Interestingly, mepolizumab alleviated not only her symptoms of asthma but also her photophobia. Moreover, the mfERG responses recovered.

Conclusions: Localized cone dysfunction in the macula was found by mfERG in the two patients who had asthma. The combination of mfERG and ffERG is important in diagnosis. Patients with asthma or eosinophilic disease may develop cone

dysfunction through autoimmune pathology. This study suggests that specifically IL-5 might play a key role in these cone dysfunctions.

9.23 A cone dystrophy in a patient with a lupus syndrome: an auto-immune retinopathy?

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Purpose: To discuss the etiology of an auto-immune retinopathy in a patient with a history of lupus treated with rituximab.

Methods: We present a case of a 50 year old woman with a history of lupus treated with rituximab and hydroxychloroquine for 8 years, who developed a rapidly evolving cone dystrophy. She had a history of atrophic maculopathy in the right eye, secondary to a probable choroidal ischemia related to lupus. In February 2016, she presented with a bilateral stellar neuroretinitis related to lupus, which resolved in a few weeks. Three months later, she complained of a loss of central vision and visual field defects in the left eye. The fundus was subnormal. Optical coherence tomography (OCT) showed outer retinal abnormalities in the left eye with a thickening of the ellipsoidal zone retrofoveolar and a disruption and a thinning of the parafoveal outer photoreceptor layers. Multifocal ERG found a disappearance of the foveolar peak whereas it had been normal few months earlier. Global ERG showed an absence of the cone response but normal rod function.

Results: Etiologic investigation of an autoimmune retinopathy was carried out, including the search for a paraneoplastic syndrome with a body scan, a PET-scan and a lumbar puncture with serum antiretinal antibody analysis. Indirect immunofluorescence on rat retina with patient's cerebrospinal fluid found retinal autoantibodies. Hydroxychloroquine was discontinued and rituximab was switched to cyclophosphamide.

Conclusions: This is a case of a retinopathy with specific cone involvement, pointing to the diagnosis of autoimmune retinopathy while taking rituximab. A paraneoplastic syndrome must be systematically investigated.

9.24 KCNV2-retinopathy diagnosed with full field ERG: a case report

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Purpose: KCNV2-retinopathy, otherwise known as "cone dystrophy with supernormal rod electroretinogram" (CDSRE), is a rare autosomal recessive disease. This case report outlines its pathognomonic features on the full field ERG.

Methods: We report ERG responses of an 8-year-old girl complaining of progressive visual loss associated with nyctalopia. Complete ophthalmological examination was performed including fundus autofluorescence imaging (FAI) and macular spectral domain optical coherence tomography (SD-OCT). The patient underwent full-field ERG (ffERG) testing according to the ISCEV standards using DTL electrodes and a Diagnosys® recording device.

Results: On the morphological level, SD-OCT revealed foveal ellipsoid zone disruptions with a periphery that appeared normal. FAI showed a mildly elevated level of AF in the foveal area. FfERG under scotopic conditions revealed very reduced responses to dim flashes, with markedly delayed implicit times of the a and b waves. The ERG to the brightest flash (10 $cd.s.m^{-2}$) showed a broadened and delayed a-wave with a "rhomboid-like" shape. There was also an abrupt increase in amplitude of the b-wave with increasing flash intensity associated with a normalization of implicit times. Under photopic conditions, responses were severely reduced with a with a marked implicit time shift for each stimulus step.

Conclusions: Full-field ERG is critical for the correct diagnosis of KCNV2-retinopathy showing

pathognomonic features which helps us to understand its pathophysiology.

9.25 New LRAT mutation and long term follow up in a fundus albipunctatus patient

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Purpose: To describe clinical and electrophysiological findings and the result of genetic testing in a 21 year old female, who we have followed with congenital night blindness since the age of 3.

Methods: At the age of 3, the patient was tested with Lea symbols and cone adaptation test and an ERG under anesthesia was performed. Outpatient testing included serial Goldmann visual fields, repeated ERG, color vision, Goldmann Weekers adaptometry, and fundus imaging. Next generation sequencing was performed for a panel of 31 genes and additional RLBP1 and RDH5 gene sequencing was obtained.

Results: At the age of 21, the patient's visual acuity was 20/20 in each eye (OD +0.50 +2.75x93, OS +0.25+2.50x86). She had an abnormal ERG, delayed dark adaptation, and a mild B/Y color vision abnormality. She was heterozygous for new mutations in LRAT c.557A>C (p.Lys186Thr) and c.197G>A (p.Gly66Glu). Both mutations are predicted to be deleterious. Parental testing confirmed that the mutations were on opposite alleles. She had normal vitamin A levels and tested negative for the three other white dot retinopathy genes involved in the retinoid cycle (RPE65, RLBP1 and RDH5).

Conclusions: We describe a new LRAT mutation in a patient with fundus albipunctatus and review her clinical and electrodiagnostic results. Treatment with 9-cis-retinoids will be considered.

Funding: Spark Initiative

9.26 Expansion of clinical spectrum of Oguchi disease

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Purpose: Describe a new clinical observation in three cases of Oguchi disease in a highly-consanguineous Egyptian family.

Methods: All patients underwent a full ophthalmological examination including visual acuity, intraocular pressures by air puff and Goldmann applanation tonometry, fundus photography in light adapted state as well as after prolonged dark adaptation (>3 hours), optic disc assessment, and automated visual field perimetry.

Results: The proband is a 66 year old man with corrected visual acuity of 0.7 bilaterally. The patient was aware of night blindness since childhood, running in his family. The fundus examination showed diffuse, golden-yellow discoloration with a metallic sheen throughout the fundus, with normal color restored after prolonged dark adaptation. He first presented with elevated intraocular pressure in both eyes (36 mmHg OU) and evident optic nerve head cupping with some field changes in the form of superior arcuate scotomata. The second case was his elder son, a 31 year old male with corrected visual acuity of 1.0 bilaterally who exhibited the same features of Oguchi disease with no cupping, normal IOPs, and normal visual field. The third case was his younger son, a 28 years old male with corrected visual acuity of 1.0 bilaterally who exhibited the same features of Oguchi disease, a suspicious disc with borderline IOPs, and suspicious field changes in the form of a superior arcuate scotoma in one eye and non-specific scotomata in the other eye.

Conclusions: Open angle glaucoma could be a new feature associated with Oguchi disease. The highly consanguineous nature of the family could be responsible for the multi-generation inheritance of an autosomal recessive condition as well as presentation of glaucoma in the family. Genetic testing to exclude the presence of other genes responsible for glaucoma in the family is pending. Further tests to confirm glaucoma in the third case

will be conducted via optical coherence tomography (OCT) of the optic nerve head as well as repetition of the visual field.

9.27 Oguchi disease: report of a case

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Purpose: To report a case of Oguchi disease and review current knowledge in the literature for this rare disorder.

Methods: A subject with a clinical diagnosis of Oguchi disease (OD) underwent ophthalmological examination including Goldman visual field assessment, electrophysiological testing according to the ISCEV standards, spectral domain optical coherence tomography (SD-OCT, and fundus autofluorescence (FAF). Based on clinical findings, we reviewed the literature on current knowledge in the disease.

Results: A 29-year-old man from Pakistan reported night vision difficulties from infancy. He had no relevant medical or family history. Best corrected visual acuity (BCVA) was 20/20 in both eyes. Goldman visual field was normal. Full-field ERG performed according the current ISCEV standard revealed a generalized severe rod system dysfunction with normal cone system function. The mfERG was also normal. Fundus examination revealed a typical golden appearance. There was, however, no pigment migration or retinal atrophy. Fundus autofluorescence was normal. SD-OCT revealed a fusion between the ellipsoid and the interdigitation zone with a preserved outer nuclear layer in both eyes. Altogether these findings are in keeping with the diagnosis of Oguchi disease which was molecularly confirmed by the identification of a homozygous change (c.577C>T p.Arg193)* in the SAG gene.

Conclusions: This report adds a new case to the current literature of this rare disorder considered as a form of congenital stationary night blindness associated with an unusual fundus appearance.

Friday 22nd June 2018, 15:30–16:15

Session 10: Paper Session – ABCA4-associated retinopathy (Stargardt)

10.01 Spatial characteristics in retinal dysfunction of ABCA4-associated retinal disorder in West China

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Purpose: Prognostic values of generalized functional phenotypes are well-established in ABCA4-associated retinal disorder. However, the spatial characteristics of retinal dysfunction are not fully known. The purpose of this study is to determine spatial characteristics of retinal dysfunction in patients with ABCA4-associated retinal disorder in west China in comparison with the generalized functional phenotypes.

Methods: Twenty-three patients with ABCA4 mutations who underwent full ophthalmic examinations were recruited. Full-field electroretinogram (ffERG) and multifocal

electroretinogram (mfERG) with real-time fundus camera monitoring were recorded incorporating the ISCEV standards. Patients were classified into three groups based on the findings of full-field ERGs: Group 1 (n=6) - dysfunction confined to the macula; Group 2 (n=5) - macular and generalized cone system dysfunction; and Group 3 (n=12) - macular and both generalized cone and rod system dysfunction. Statistical analysis was performed between groups in terms of clinical parameters: age, age of onset, and the logarithm of the minimum angle of resolution visual acuity (logMAR VA). Decline rate for P1 amplitude of mfERG was calculated by comparing to a normal control group. In order to investigate the spatial characteristics, decline rate in the total recoded area and in the eccentric ring groups (rings 1-2, rings 3-4, and rings 5-6) was compared between ffERG groups. One eye was randomly selected for the analysis.

Results: The average age/age of onset for Groups 1, 2, 3 was 20.0/12.0 years (range, 13.0-24.0/9.0-16.0), 29.0/18.0 (range, 13.0-49.0/9.0-47.0), and 40.0/18.0 (range, 20.0-74.0/10.0-46.0), respectively. The logMAR VA for the selected eyes for Groups 1, 2, and 3 were 0.93, 1.30, 1.35 (range, 0.52-1.3, 0.82-2.0, 0.05-3.0), respectively. No significant group differences in age of onset or logMAR VA were revealed in duration. Central retinal mean thickness at the fovea (CRT 1mm) was 91μm in Group1, 139 μm in Group 2, and 116 μm in Group 3, showing a significant difference between Groups 1 and 2. The total averaged amplitude decline rate of mfERG P1 responses was 61.88% in Group 1, 66.24% in Group 2, and 89.4% in Group 3. Mean decline rates in rings 1-2, rings 3-4, and rings 5-6, respectively, were 80.03%, 80.31%, and 40.52% in Group 1, 73.27%, 69.38%, and 60.77% in Group 2 and 85.98%, 86.89%, and 90.01% in Group 3. There were significant differences between groups in terms of spatial trends of mfERG eccentric decline rate. (Recall that the groups were based on ffERG findings.)

Conclusions: Group 2 has the lowest P1 decline rate in ring 1-2， possibly due to having the largest remaining foveal thickness (CRT) among the groups. The spatial range of retinal dysfunction differed based on the ffERG groups. The mutual relations between groups of generalized dysfunction and spatial range of retinal dysfunction was confirmed, indicating that the predominant dysfunction in the central cone expands to the peripheral rod photoreceptors in ABCA4-associaed retinal disorder.

10.02 A prospective natural history study of ABCA4-related retinopathy: electroretinogram results

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Purpose: In anticipation of clinical trials, the National Eye Institute (NEI) in 2012 initiated a prospective, natural history study of ABCA4 retinopathy (clinicaltrials.gov: NCT01736293) to formulate outcome measures suitable for such trials. The growth of the atrophic lesion in ABCA4 patients over time, as documented on autofluorescence, has been used to quantify progression of retinopathy in this disease. However, the growth of the atrophic lesion cannot be followed in all ABCA4 patients, particularly those with advanced retinopathy. The ERG may be used to assess retinal function in advanced retinal disease. Here we describe the changes in ERG from our cohort of ABCA4 patients over a period of 3-4 years.

Methods: Sixty-four patients aged 12 to 67 years (median 35 years) with confirmed ABCA4 mutations were enrolled at the NEI. Best corrected visual acuity (BCVA) was measured. ERGs were recorded with Burian-Allen electrodes according to ISCEV standards, with an additional bright flash. ERG amplitudes were logged and percentage change per year was calculated. Color discrimination thresholds were measured along eight axes in CIE 1976 L*u*v* space, using the low-vision Cambridge Color Test (CCT). Dyschromatopsia was quantified from achromatic area (106 u*v*2), calculated as the area inside the polygon formed by connecting thresholds.

Results: Functional measurements at baseline confirmed the heterogeneity of our ABCA4 cohort. DA3 b-wave amplitude spanned a six-fold range along a continuum from 131 to 654 μV (median 348 μV). LA3 amplitude ranged from absent to 187 μV (median 106 μV), and LA3 implicit time similarly varied along a continuum from 29.5 to 56.0 msec (median 34.0 msec). The histogram of BCVA had two peaks, one at 20/25-20/32 and the

other spanning 20/100-20/200. Forty-six eyes (72%) had a BCVA of 20/100 or worse. Achromatic area on CCT spanned greater than a 100-fold range, from 17 to 7653 106 u*v*2 (normal<70). At baseline, all scotopic and photopic stimulus parameters were correlated with achromatic area ($p<0.0001$, $R^2>0.39$ for all). Longitudinal ERG data spanning 3 or 4 years were available from 38 patients: 17 with 3 years of follow-up and 21 with 4 years of follow-up. The rate of change in ERG amplitudes was consistent across the DA3, DA30 and LA3 stimuli, with a mean (±SD) reduction of 5.0%/year±6.4%/year. The rate of change in ERG amplitude was considerably more variable for the DA0.01 (6.5%/year±10.9%) and 30Hz (6.9%/year±12.0%) stimuli. Twelve patients (32%) had greater than 8.5% reduction in amplitude/year, which would result in at least a 30% loss in amplitude over 4 years.

Conclusions: Patients with ABCA4-related retinopathy have heterogeneous changes in retinal function and structure that progress slowly over time. As such, it is unlikely that one functional or structural measure can be found to quantify disease progression in all patients. We describe the rate of reduction in ERG amplitude over a period of 3-4 years, which may serve as an outcome measure in a proportion of patients with ABCA4-related retinopathy.

10.03 Clinical and genetic characteristics of East Asian patients with Stargardt disease; EAStar Report No. 1

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Purpose: East Asia Inherited Retinal Disease Consortium (EAIRDC) was established in 2016 to understand the etiology of IRD in a large cohort of East Asian patients assumed to have similar genetic background. Here, we describe the clinical and genetic characteristics of the cohort of East Asian patients with Stargardt disease (STGD1).

Methods: Forty-five participants from 43 families with a clinical diagnosis of STGD1 and harbouring at least one pathogenic ABCA4 variant were enrolled from three centers, one in Japan, one in China, and one in South Korea. A detailed history was obtained and comprehensive ophthalmological examinations including electrophysiological assessment were performed. In silico analysis was performed in all detected ABCA4 sequence variants. A genotype-functional phenotype association was investigated between genotype grouping (Groups A, B, and C) and electrophysiological grouping (Groups 1, 2 and 3).

Results: Twenty families from Japan, 16 from China, and 7 from South Korea were recruited. The median age of onset was 12.0 (range 5-70) years and the median age at the latest examination was 27.5 (range 11-85) years. The median logarithm of the minimum angle of resolution visual acuity

(logMAR VA) in the right and left eye was 0.82 (range, 0-2.28) and 0.82 (-0.18-2.28), respectively. Patients were classified into three groups based on the findings of full-field ERGs: Group 1 (n=18) – macular dysfunction; Group 2 (n=4) - macular and cone dysfunction; and Group 3 (n=14) - macular and cone/rod dysfunction. Fifty-nine pathogenic ABCA4 variants were identified including 20 novel variants. There are six patients in genotype Group A (multiple nulls), 13 in genotype Group B (null + non-null), and 19 in genotype Group C (multiple non-nulls). A significant association was revealed between electrophysiological grouping and genotype grouping (p=0.04191, Chi square test).

Conclusions: Clinical and genetic heterogeneity has been documented in an East Asian cohort with STGD1. A significant genotype-functional phenotype association has been identified in the East Asian population.

Friday 22nd June 2018, 16:15–17:15

William Dawson Memorial Lecture

Is electrophysiology necessary for the diagnosis of inherited retinal dystrophies at the time of multimodal imaging?

Professor Isabelle Meunier

Centre National de Référence Affections Sensorielles Génétiques, Montpellier, France

Saturday 23rd June 2018, 08:00–09:30

Session 11: Paper Session – Methods & Innovation III: Retina and ERG

11.01 Impact of gaze and electrode position on ERG morphology

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*these authors contributed equally to the study

Purpose: We have previously shown that the multi-angular ERG (maERG), a new recording technique based on a multi-electrode and multi-gaze approach, yields ERG responses of different morphologies that can be used to build retinotopic maps of retinal function. The purpose of this study was to further analyze these morphological differences in order to determine if they could also help us localize the intraretinal origin of the different components of the corneal ERG.

Methods: Photopic ERG recordings were obtained from OD in normal subjects (n=10) using three skin or HK-loop electrodes placed at the center of the eye and at the external and internal canthi [directly on the conjunctiva (HK-loop) or on the adjacent skin (skin electrodes)]. Subjects were asked to look at 11 different gaze positions (40° nasal to 40° temporal). Results were compared to focal (from limbus to optic nerve) ERGs recorded directly on the sclera of anaesthetized and paralyzed New-Zealand rabbits. ERG morphologies were assessed in the time-frequency domain with the Discrete Wavelet Transform (DWT). Emphasis was put on the %OPs descriptor, as established in Gauvin et al. (*Biomed Res Int* 2016;1-12).

Results: In recordings obtained with the central electrode, we noticed negligible changes in ERG morphologies with gaze position (%OPs≈47%). In contrast, when the eye gazed away from the recording electrodes, we noticed a significant increase in %OPs values, the latter being most obvious in recordings obtained with the HK-loop (from 47.4% to 64.0%). Similar results were also obtained in rabbits where the %OPs increased from 38.0% (cornea) to a maximum of 77.8% (midpoint between the cornea and the optic nerve) before decreasing to 56.4% (near the optic nerve). The latter decrease was not observed in human subjects, most probably due to limitation in

gaze range. In all instances the gradual growth in %OPs was accompanied by a significant reduction in a- and b-wave descriptors.

Conclusions: Our study demonstrates that the ERG morphology (of human and rabbit) gradually changes from a slow wave dominated response (with typical a- and b-waves) to one that is almost exclusively made of fast oscillations (i.e., OPs) as the recording electrode is moved away from the cornea to the back of the eye. In human, this phenomenon is best demonstrated in recordings obtained using the HK-loop electrode since its direct contact with the eye permits a higher signal-to-noise ratio compared to the skin electrode. We believe that this relative enhancement of the OPs combined with a reduction in b-wave amplitude obtained when moving the electrode from the cornea towards the optic nerve could suggest that the OP and a- and b-waves dipoles are orthogonally distributed within the retina, a claim that we are currently investigating.

Funding: CIHR.

11.02 Comparison of the pattern ERG and uniform field ERG in humans

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Purpose: The PERG is the electroretinal response to contrast reversal of pattern stimuli that reflects functional integrity of retinal ganglion cells and their axons. The uniform field electroretinogram (UF-ERG) to stepwise luminance modulation of low temporal frequency allows the separation of responses to light increments and decrements (R. Viswanathan et al. *Invest Ophthalmol Vis Sci* 2000; 41:2797-2810) and has been described in non-human primates with experimental glaucoma. The UF-ERG has not been previously described in human subjects.

Methods: In 18 human subjects (36 eyes) aged 20-75 years, the UF-ERG and PERG were recorded. For UF-ERG luminance modulation was provided by an 800x600 pixel OLED stimulator (Diagnosys LLC) subtending a 24x32 degree viewing angle producing a luminance of 300 cd/m^2 for a 200 msec duration. 220 replications of 230 msec sweep duration were obtained at both stimulus onset and stimulus offset and averaged. The PERG was recorded to 0.8 degree checks at 2 reversals/second; 150 sweeps were signal averaged.

Results: For the P50 component, there was a significant difference between UF-ERG and PERG in peak latency ($p<.0001$) between UF-ERG and PERG. No significant difference between UF-ERG and PER was found for the N95 component peak latency nor for P50 or N95 amplitude measures.

Conclusions: The UF-ERG can be reliably recorded in human subjects. The response is similar in amplitude to the PERG P50 and N95 components. The advantage of using a non-patterned stimulus which does not require steady fixation and refractive correction make the UF-ERG an ideal stimulus for clinical investigation of optic neuropathy.

11.03 Little effect of 0.01% atropine eye drops on the PERG

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Eye Center, University of Freiburg Medical Center, Freiburg, Germany

Purpose: Previous studies in psychiatric patients suggest that PERG amplitudes are modulated by alterations in retinal dopamine. Atropine eye drops, which appear to be effective in reducing myopia progression, likely act by triggering an increased release of dopamine. It is thus plausible that atropine eye drops should have an effect on PERG amplitudes. The aim of the present study was to test this, using the difference in amplitude between contrast levels and the ratio of amplitudes between check sizes as primary endpoints.

Methods: Fourteen subjects with no more than ±2 diopters of ametropia and distance acuity of at

least 1.0 participated. In each subject one eye was randomly selected for atropine application (one drop of 0.01% atropine solution once daily for 14 days). Two sets of steady-state PERG recordings were performed, one with different contrasts (25% and 98%), as in previous studies in psychiatric patients, and one with different check sizes (0.8° and 17°), as used for retinal ganglion cell testing in glaucoma screening. Other relevant measures, including near acuity, near-point distance, and pupil diameter were also obtained.

Results: No atropine-related changes of PERG amplitude were found in the recordings to different contrasts. The amplitude difference between contrast levels increased slightly (by 6%), but not significantly (p=0.08) with atropine application. In the check size condition, raw amplitudes increased after atropine application by 17% (p<0.01) and 10% (p<0.03) for large and small checks, respectively. However, the ratio of amplitudes did not change significantly. Among the additional measures, pupil size changed significantly (median change 0.5 mm; p<0.002). However, there was no significant correlation between changes in pupil size and PERG effects in any of the recording conditions.

Conclusions: The change in PERG primary endpoints after 14 days of atropine administration was small (in particular when compared to the effects in depression) and not statistically significant. We found inconsistent evidence of changes in PERG raw amplitude. In summary, 0.01% atropine eye drops as used for myopia prevention appear not to have a large impact on retinal processing as reflected by the PERG.

11.04 Effect of atropine on human multifocal electroretinogram responses to defocus

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Purpose: Despite the global use of atropine in myopia control, the mechanism by which atropine acts to inhibit the progression of myopia is still unclear. This study investigates the effect of atropine on the human global flash mfERG under conditions of retinal defocus.

Methods: Global flash mfERG responses were recorded monocularly in the non-dominant eyes of 19 healthy subjects (age 23±4 years) on a RETIScan system (Ronald Consult, Wiesbaden, Germany) using a 61-element hexagonal stimulus array scaled for eccentricity. Recordings were obtained under three randomised conditions of retinal defocus: 2.00 D myopic defocus, 2.00 D hyperopic defocus and no defocus using full-aperture ophthalmic lenses after correcting for testing distance. Each defocus condition was tested prior to the instillation of atropine and then again 24 hours after instillation of 1 drop 0.1% atropine. Signals reflecting activity from outer and inner retinal layers – direct (DC) and induced (IC) components, respectively – were analysed separately. The mfERG responses were pooled within central (0° to 6°) and peripheral (6° to 24°) retinal zones and compared across the experimental conditions, relative to the baseline (i.e. no defocus, no atropine condition).

Results: Within the central zone, atropine had no effect on the amplitudes and implicit times of the DC or IC responses to defocus. Within the peripheral zone, atropine had a significant main effect of increasing DC amplitude ($F_{1,18}=7.821$, $p=0.012$) and implicit time ($F_{1,18}=15.406$, $p=0.001$) in response to defocus. For the IC responses, there was a significant interaction effect of atropine and defocus ($F_{2,36}= 6.050$, $p=0.011$) with greater post-atropine amplitudes under myopic defocus (mean difference= 15.52%, 95% CI= 5.627 to 25.421, $p=0.004$). Atropine also had a significant main effect of increasing IC implicit time ($F_{1,18}= 9.722$, $p =0.006$).

Conclusions: Our results imply that atropine acts in the peripheral retina to enhance mfERG responses in areas of the retina experiencing myopic defocus. These findings suggest that atropine may potentiate the effects of myopic defocus in inhibiting axial eye growth and myopia.

11.05 Muscle activity as a symptom of photophobia in the ERG signal

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Purpose: Photophobia is a symptom associated with many ophthalmological and neurological conditions and is expressed by intolerance to light. Despite its frequent presentation, research into this condition has been hampered by a lack of a quantitative method to evaluate the severity of the condition and its correlation with other symptoms, conditions, or treatments. As the most common presentation of the symptom is manifested by muscle eyelid activity, the purpose of this study was to evaluate how this reflexive movement can be reflected and quantified in the ERG signal.

Methods: A retrospective analysis of the records of patients undergoing routine clinical full-field ERG testing at USF was conducted. Only dark-adapted oscillatory potential responses (OPs), recorded as part of a standard ISCEV protocol using an LKC UTAS-E3000 system and DTL electrodes, were analyzed. The inclusion criteria were: age $\geq$18 years and relatively overall good quality of the signal. The 30 msec pre-stimulus baseline was used to establish noise baseline. The signal was analyzed within the time period 50 -160 msec after the stimulus. The 50 msec criterion was used because by that time, the OP activity was greatly diminished or absent, while the 160 msec criterion was used to avoid ambiguity potentially caused by voluntary muscle activity. The amplitude of the muscle activity was measured as RMS in 10 msec bins within the time period for each of 9 runs; the values were averaged cross all runs and area under the curve (AUC) was calculated and peaks determined using GraphPad Prism 7.0.

Results: The records of 30 patients referred for a full-field ERG during the period January 2015 to January 2016 were screened and the records of 19 patients (38 eyes; 8 males and 11 females; age 51.4$\pm$ 7.8 years) met the inclusion and exclusion criteria and were selected for further analysis. Although slight individual differences were noted, the peak area under the curve did not differ between right eyes (462$\pm$536 μV^2) and left eyes (413$\pm$408 μV^2; $p>0.05$, Wilcoxon paired test). Therefore, values from both eyes were subjected to cluster analysis, which showed three clusters with AUC centroids at 172 (n=26), 1014 (n=11) and 2257 μV^2 (n=1), respectively. The four patients with highest AUC values reported photophobia symptoms. Analysis of the peaks showed that most activity was centered around two time periods: ~75 msec and ~140 msec, with more activity measured during the first time period.

Conclusions: Using the ERG signal during dark-adapted OP recording may be useful in documenting eyelid muscle activity likely related to photophobia. We are in the process of analyzing a larger dataset to investigate further the feasibility of this approach.

11.06 Corneal potential maps recorded from healthy human eyes

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Purpose: Following a visual stimulus, the spatial distribution of the response at the retina determines the spatial distribution of ERG amplitudes recorded at the cornea. Measurement of the local corneal ERG amplitudes may, therefore, provide useful clinical information in cases of local retinal dysfunction (e.g. early progressive disease) or local rescue of retinal function (e.g. local gene therapy treatment). A contact lens electrode array was previously developed for rat and used to record multi-electrode ERG (meERG) responses before and after experimental retinal lesions. Here, a similar approach is described for obtaining meERG responses from human eyes. Early results comparing responses recorded under dark-adapted (DA) and light-adapted (LA) conditions are reported.

Methods: A contact lens electrode array (CLEAr Lens) was fabricated using an acrylic substrate. The surface that touches the eye has corneal and scleral base curves, similar to a scleral contact lens. The scleral contact area is thin so that the eye lids close over this portion, to stabilize the lens. The area over the cornea is thicker and planar on the distal side; the vertical side walls of this area prevent pupil obstruction by the eye lids. A thin-film parylene cable containing 33 platinum

electrodes (100 μm diam) is bonded to the planar side of the acrylic substrate. Through-holes in the substrate, from the corneal surface to the distal surface, are filled with saline solution and serve as conductive bridges from the cornea to the platinum electrodes. Full-field flashes were presented under DA and LA conditions to normally sighted subjects; each flash resulted in up to 33 ERG waveforms recorded simultaneously. ERG a-wave and b-wave amplitudes were evaluated for each electrode channel. A three-dimensional spline was used to interpolate between the 33 locations over the entire corneal surface, resulting in a continuous corneal potential map. Each map was normalized by converting to standard score values and difference maps (DA-LA) were created.

Results: The CLEAr Lens was easy to insert, and stable on the eye during recording. Small air bubbles beneath the lens did not affect the overall recording quality. For subjects with flatter corneas, an air bubble would form above the cornea during recording. For subjects with less of the eye exposed when the lids were in a natural open position, the lens could be pushed off-center by the lids. Channel yield ranged from 24-33 (73%-100%). Noise was highly correlated across channels. Flash-to-flash variability in a-wave and b-wave amplitudes was similar to conventional ERG recording, but relative amplitude differences across the cornea (i.e. the map of interpolated standard score values) was very consistent from flash to flash. Consistent differences were observed between DA and LA responses.

Conclusions: Recording meERG responses from human subjects using the current CLEAr Lens design is feasible, though engineering challenges remain, including the awkward tethering of the lens to the amplifier, inconsistent channel yield, and requirement for accurate lens fit to each subject. Strengths of the approach include excellent signal quality and measurement of an accurate corneal potential map following a single full-field flash.

Saturday 23rd June 2018, 11:30–13:00

Session 12: Paper Session – Electrophysiology along the optic pathway

12.01 Visual evoked potentials in patients with inherited optic neuropathy

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Purpose: In patients presenting with visual loss, visual evoked potential (VEP) responses enable us to evaluate optic nerve function. The purpose of this study was to analyze VEP responses in a series of patients with inherited optic neuropathy referred to a neuro-ophthalmologic clinic.

Methods: Patients referred between January 1st 2016 and December 2017 with inherited optic neuropathy were retrospectively included. In all patients undergoing VEP, the electrophysiological results were compared with clinical examination and ocular coherence tomography findings. Flash and pattern VEP recording with different check sizes (60', 30', 15', 7') was performed.

Results: Sixty-eight patients met the inclusion criteria and 27 had undergone flash and pattern VEP on presentation. On clinical examination, the optic disc was noted to be either as pale or unremarkable by the referring ophthalmologist. Two different situations were encountered: (i) in 7 patients (13 eyes) with Leber's Hereditary Optic Neuropathy (LHON) who presented with an acute visual loss in at least one eye, no pattern VEP responses were obtained and the temporal RNFL thickness was normal or increased; (ii) in 20 patients, the visual loss was slowly progressive with two subgroups regarding the VEP results: in 21 eyes, an undetectable pattern VEP P100 response was associated with a reduced mean temporal RNFL of 37.1 μm (range 21-43); in 19 eyes, a P100 response could be obtained (at least with a 60' check) and the mean temporal RNFL thickness was also reduced: 40.7μm (range 22-60). The difference in temporal RNFL thickness was not statistically significance (p=0.12). The genetic testing in these patients enabled us to diagnose either autosomal dominant optic neuropathy or slowly progressive LHON.

Conclusions: Visual evoked potential is helpful in objectively demonstrating vision loss in patients with a normal or a subnormal appearance of the optic disc and normal RNFL thickness as encountered in acute LHON. In progressive visual loss such as autosomal dominant optic neuropathy, the VEP responses enabled us to evaluate the functional status which appears to be independent of the temporal RNFL thickness.

12.02 Photopic negative responses (PhNR) of patients with mild traumatic brain injury (mTBI)

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Purpose: The photopic negative response (PhNR) is a slow negative potential of retinal ganglion cell origin in the cone-mediated flash ERG. The purpose of this study was to examine whether the PhNR is altered in patients with a diagnosis of mild traumatic brain injury (mTBI).

Methods: PhNRs were recorded using DTL fiber electrodes with a Ganzfeld System (Diagnosys LLC) from 11 patients with mTBI (20-49 years of age) and 21 control subjects (20-50 years of age). Stimuli consisted of brief (<5 ms) red flashes ranging from -2.2 to 0.8 log phot cd.s/m^2 on a 2 log scot cd/m^2 blue background. The PhNR amplitude was measured at its trough from baseline;, the b-wave, which originates from cone bipolar cell activity, was measured at its peak from the preceding a-wave. Both PhNR and b-wave amplitude were plotted as a function of flash intensity and fitted with the Naka-Rushton equation of the form V(I)=(Vmax*I^n)/(I^n+K^n), where V is the response at intensity I, Vmax is the saturated amplitude, n is the slope, and K is the semi-saturation constant (intensity at 50% of Vmax). Vmax, n and K derived from the fits were compared between mTBI patients and controls.

Results: For the PhNR intensity response function, K was significantly smaller (p=0.036) for the mTBI patients relative to control subjects (0.13 vs 0.2). Vmax and n demonstrated a tendency to be larger for the mTBI patients relative to control subjects, but these differences were not statistically significant. None of the Naka-Rushton fit parameters of the b-wave differed significantly between mTBI patients and control subjects.

Conclusions: Reduced values for the semi-saturation constant may indicate elevated sensitivity of the cellular generators of the PhNR in patients with mTBI suggesting retinal involvement in mTBI patients.

12.03 Structure- function relationship in glaucoma suspect and early open angle glaucoma

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Purpose: To investigate the relationship between functional tests such as static automated perimetry (SAP) as a subjective method and multifocal electroretinogram mfERG as an objective method and a structural imaging test, optical coherence tomography (OCT), in primary open angle glaucoma suspects and in patients with early primary open angle glaucoma (POAG).

Methods: Sixty eyes of 31 individuals were included. Group 1: 20 eyes of 10 glaucoma suspects; Group 2: 20 eyes of 11 patients with early POAG; Group 3: 20 eyes of 10 healthy individuals. After complete ophthalmic examination, Humphrey visual field analysis (HFA), mfERG, and spectral domain OCT were performed. These examinations were performed three times at 3-month intervals; only results from the last examination were used for the analysis. The data used in analysis were both global and hemispheric (superior and inferior hemispheres) to facilitate the analysis and make it more reliable as the correlation was done between the corresponding areas of the retina which were assessed by HFA, mfERG, and OCT.

Results: In the glaucoma suspect group, there was a statistically significant difference from normal subjects in structural measures including RNFL and GCC thickness (average and hemispheric). For functional measures, mean deviation (MD) of HFA was significantly different between glaucoma suspects and normals. For the mfERG, the only

significant difference between glaucoma suspects and normal subjects was in P1 response amplitude density (RAD) of the inferior hemisphere of the retina. In the early POAG group, there was a statistically significant difference from normal subjects in OCT measures including both peripapillary RNFL and GCC thickness. There were also significant differences between the two groups in MD of HFA. Regarding functional mfERG changes, there was a significant difference in P1 RAD, both global and hemispheric, between early POAG patients and normal subjects. Comparison of structural and functional measures in glaucoma suspects versus early POAG patients indicated a significant difference between the two groups in the average and inferior hemisphere RNFL and GCC thickness but no difference in superior hemisphere RNFL and GCC thickness. The only significant functional difference between the two groups was HFA MD of the superior hemisphere. There were no significant differences in mfERG findings between the glaucoma suspects and the early POAG patients.

Conclusions: The use of multiple functional and structural tools can help to diagnose POAG early in the course of the disease with possible implications for the underlying pathophysiology.

12.04 Which ERG measures identify ganglion cell deficits? A study of uniocular optic nerve hypoplasia (ONH)

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Purpose: Several ERG features, such as the PERG N95 component, steady-state PERG amplitudes, and full-field, photopic negative responses (PhNR), are associated with declining ganglion cell function in glaucoma and other optic nerve diseases. We investigated ERGs to a range of stimuli in congenital optic nerve hypoplasia (ONH) with moderate to severe ganglion cell deficits in one eye.

Methods: Participants were 11 children with ophthalmoscopically diagnosed uniocular ONH. On fundus photographs, the ratios of disk diameter to disc-macula (DD:DM) were ≥0.34 in the fellow eyes (normal to borderline) and 0.21 to 0.10 (moderate to severe ONH) in the affected eyes. In one session before 26 months of age, we recorded ISCEV Standard (3.0) and strong (10) light-adapted ERGs, 30 Hz flicker ERGs, and PERGs for three check sizes (0.4°, 0. °9° and 2°) using chloral hydrate sedation, cycloplegia, and a refractive correction incorporating the stimulus distance. Extended ERG protocols were completed in five participants for ON- and OFF-responses, PhNRs to red flash on a blue background, and steady-state (ss) PERGs (16.7 Hz) to large and small checks.

Results: At 5 years of age, visual acuity in the fellow eyes ranged from 0.0 to 0.30 logMAR (6/6 to 6/12); function in the affected eyes ranged from gross motion perception to no light perception. Full-field ERGs were robust in all eyes; a-waves, b-waves, d-waves and i-waves showed no association with the severity of ONH. PhNRs to moderate and strong red flashes (1.0 to 6.0 cd.s.m-2) were markedly diminished in the affected eyes relative to the fellow eyes ($p<0.001$); differences did not reach significance for white flashes or for the weak blue flash (0.3 cd.s.m-2). PERGs in the affected eyes showed marked deficits in the N95 amplitude for 0.9° and 2° checks; P50 was inconsistently affected but a smaller P50 was associated with earlier implicit times across all eyes. Our assessment of PERGs to small checks and of ssPERGs was inconclusive; some non-significant waveforms were recorded in both affected and fellow eyes in this small study.

Conclusions: The PhNR to chromatic stimuli and the PERG N95 component to supra-threshold checkerboards were both sensitive indicators of the severity of ONH. This suggests that ganglion cell dysfunction rather than elevated pressure or other vascular or neurodegenerative processes are reflected in these responses. We find no evidence for a substantial ganglion cell contribution to standard ERG measures or to ON or OFF responses of the retina.

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12.05 Toward a more sensitive method to detect chiasmal misrouting

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Purpose: Chiasmal misrouting is established in albino patients using onset or flash VEPs. Often used methods to determine misrouting are to calculate the Pearson's correlation coefficient (Song et al. *J AAPOS* 2000;4:302-10) or the chiasm coefficient (Jansonius et al. *J Neuro-Ophthalmol* 2001;21:26–9; Pott et al. *Doc Ophthalmol* 2003;106:137–43) from the O1-O2 signals when stimulating OD and OS separately. A negative coefficient means there is a correlated asymmetry in the signals to each hemisphere, indicating misrouting. Sometimes misrouting cannot be shown convincingly in albino patients using these correlation methods. This might mean that misrouting is not present in all albino patients, that the sensitivity of the test is not 100%, or both. We investigated if the conventional VEP misrouting detection method can be optimized/modified to become more sensitive.

Methods: The determination of the chiasm coefficient (CC) has been optimized/modified in three ways: (1) by low pass filtering the O1-O2 signals using a brick-wall filter, (2) by adjusting the window over which the coefficient is calculated, and (3) by subtracting part of the OU O1-O2 signal from both the OD and OS signal to correct for possible asymmetry in the position of the O1 and O2 electrodes and/or hemispheric asymmetry of the visual cortex. For this study, we included 74 patients ≥6 years old who were diagnosed with albinism between 2011 and 2016 and who underwent a standard ISCEV VEP onset protocol (60' check size) for OD, OS, and OU. As controls, we used 17 patients diagnosed with functional vision loss and the same inclusion criteria. Besides calculating the CC for different low pass filtering cutoff frequencies, different windows, and different amounts of OU subtraction, we also determined the percentage of albino patients and controls who would be classified as having misrouting if a cutoff CC of -0.2 would be used. Optimization was mainly based on the percentages of misrouting for both the albino (high percentage) and control group (low percentage).

Results: Optimization resulted in the following parameters: calculation window 60-200 ms, low pass filter cutoff 25 Hz, and a (predicted) 50% OU subtraction. CC was averaged over all patients. For the albino patients, the results were standard calculation: CC=-0.43 and percent misrouting=74.3% (55/74); optimized calculation: CC=-0.71 and percent misrouting=89.2% (66/74). For the controls, the results were standard calculation: CC=+0.52 and percent misrouting=0.0% (0/17); optimized calculation: CC=+0.45 and percent misrouting=5.9% (1/17). The reason one control subject had a CC<-0.2 (from +0.53 to -0.60) was mainly due to the subtraction of 50% of the OU signal.

Conclusions: Optimization/modification of the calculation of the CC seems to improve the sensitivity of the misrouting detection considerably. Actual sensitivity and specificity values remain to be determined after additional VEP check sizes, VEP flash, type of coefficient, and cut-off value of the coefficient have been analysed and taken into account.

12.06 Acuity VEP: the potential for machine learning

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Purpose: VEP approaches to estimate visual acuity basically all use the information obtained across a number of check sizes (or spatial frequencies) to derive a measure of acuity. Amplitude is always used, sometimes combined with phase or a noise measure. In our approach, we employed steady-state brief-onset low-contrast checkerboard stimulation and obtained amplitude and significance for six check sizes, yielding 12 values. The rule-based "heuristic algorithm" (Bach et al. 2008) yielded a testability of over 95% and a limit of agreement (loa)=0.18 logMAR between behavioural and objective acuity in 109 eyes (healthy, artificially reduced vision, and patients). We here aimed to test whether a neural network employing machine learning on this relatively small dataset could achieve a similar loa.

Methods: Given recent advances in machine learning, we applied a wide class of neural network

(nn) algorithms to this data set. This was done within the “caret” framework of R using the methods rf (random forest), glm, xgbLinear, deepnet and many more. For cross-validation, using a jackknife (one-leave-out) approach, we predicted each case based on the nn having been trained on the remaining 108 cases.

Results: When using the full dataset to train, the prediction was nearly ideal, obviously an example of overfitting given the high number of free parameters within the nn. The more appropriate cross-validation method yielded an loa of ≈0.2 logMAR or worse for all nn algorithms tested. Testability, however, was 100%. We then combined the rule-based heuristic with the nn outcome by replacing missing heuristic outcomes with the nn outcome. This raised the testability to 100% without compromising loa.

Conclusions: The results of machine learning would improve with a larger database. However, machine learning approaches, especially “deep learning”, requires data sets many orders of magnitude higher than the one we used. One disadvantage is the necessity to retrain when using different check sizes. Here, by combining the rule-based heuristic with machine learning, VEP acuity reaches 100% testability with an loa of ≈0.2 logMAR.