North American Neuro-Ophthalmology Society

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JW Starr Pass Marriott • Tucson, Arizona

PLATFORM SESSION II

Tuesday, March 1, 2016 • 7:30 am - 12:00 pm

Moderators: Madhu Agarwal, MD and Timothy McCulley, MD – before the break

Moderators: Beau B. Bruce, MD, PhD and Heather Moss, MD, PhD – after the break

7:30 am - 7:45 am	Philip S. Garza Handheld Ocular Fundus Photography in Acute Subarachnoid Hemorrhage (SAH): The FOTO-ICU Study
7:45 am - 8:00 am	Kenneth S. Shindler Neuroprotective Effects of ST266 in Experimental Optic Neuritis
8:00 am - 8:15 am	Amulya Gampa Change in Peripapillary Bruch's Membrane Shape Can Be Detected 1 Hour After Lowering of Intracranial Pressure by Lumbar Puncture
8:15 am - 8:30 am	Dean M. Cestari Demographic, Systemic and Ocular Features of Non-Arteritic Anterior Ischemic Optic Neuropathy in a Large US Claims Beneficiary Database
8:30 am - 8:45 am	Michael S. Lee The Effect of Pupillary Dilation on Strabismus Measurements in Adults
8:45 am - 9:00 am	Jaydeep Kachhela Wilbrand's Knee Revisited
9:00 am - 9:15 am	Byron L. Lam Cranio-Spinal CSF Redistribution Before and Following Lumbar Puncture in Patients with Idiopathic Intracranial Hypertension
9:15 am – 9:30 am	Update: The Journal of Neuro-Ophthalmology Lanning Kline, MD, Editor-in-Chief & Jason Roberts, PhD, Managing Editor
9:30 am - 10:00 am	**Coffee Break: Arizona Ballroom**
10:00 am - 10:15 am	Alexandra Sinclair Glucagon Like Peptide-1 (GLP-1) Reduces Cerebrospinal Fluid Secretion and Intracranial Pressure: A Novel Treatment for Idiopathic Intracranial Hypertension?
10:15 am - 10:30 am	Catherine Vignal Recombinant AAV2 Containing the Wild-Type ND4 Gene (rAAV2/2-ND4) is an Experimental Gene Therapy for Vision Loss in LHON Due to the ND4 Mitochondrial Mutation: Phase I/IIa Safety Investigation Results and Upcoming Pivotal Phase III Efficacy Studies

10:30 am - 10:45 am	Ruben Torres-Torres Light Evoked Retinal Activation is Metabolically Coupled to Increases in Human Retinal, Choroidal and Optic Nerve Head Blood Flow Measured Simultaneously by Laser Speckle Flowgraphy
10:45 am - 11:00 am	David Fell A Novel Approach to Measuring Peripapillary Retinal Perfusion in Papilledema: A Pilot Study Using Optical Coherence Tomography Angiography
11:00 am - 11:15 am	Shaobo Lei The Effect of Red Light Exposure on the Pre-Existing Melanopsin-Driven Post-Illumination Pupil Response
11:15 am - 11:30 am	Ming-Hui Sun Experimental Anterior Ischemic Optic Neuropathy in Diabetic Mice Exhibited Severe Retinal Swelling and Subretinal Fluid Accumulation Acutely and More Severe Thinning Chronically
11:30 am - 11:45 am	Rachel Mercer Change in the Deflection of the Neural Canal Opening Away from the Vitreous and Towards the Retrobulbar Space as an Indicator of Treatment Efficacy of Optic Nerve Sheath Fenestration and Non-surgical Treatment for Idiopathic Intracranial Hypertension (IIH)
11:45 am - 12:00 pm	Jason J.S. Barton The Localization and Patterns of Dyschromatopsia: A Study of Prosopagnosic Subjects

**Please note that all abstracts are published as submitted.*

Tuesday, March 1, 7:30 - 7:45 am

Handheld Ocular Fundus Photography in Acute Subarachnoid Hemorrhage (SAH): The FOTO-ICU Study

Philip S. Garza[1], Caroline Fajoles-Vasseneix[1], Lindsay Clough[1], Kevin R. Sitko[1], Prem Kandiah[2,3], Nancy J. Newman[1,2,3], Valérie Biousse[1,2], Owen B. Samuels[3,2], Beau B. Bruce[1,2,4]

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Introduction:

Intraocular hemorrhage (IOH) among SAH patients (Terson syndrome) has been suggested as a risk factor for poor clinical outcomes, but this association remains debated.[1,2,3] Our goal was to assess IOH's prevalence and to evaluate its association with ICU length of stay (LOS) and in-hospital morbidity/mortality.

Methods:

Patients admitted to our neurosurgical ICU from 9/2014-7/2015 with a primary diagnosis of acute SAH were included. Bedside handheld mydriatic fundus photography was performed early after admission (median=1.5 days, IQR=1-3) and intermittently throughout the hospitalization. Fundus photographs were reviewed for IOH. Poor outcome was defined as death, care withdrawal, or discharge Glasgow Outcome Score ≤3. Multivariable logistic and Cox models were used to evaluate associations between IOH and poor outcome/LOS, controlling for age, sex, race, APACHE II score, Hunt & Hess score, respiratory failure at ICU admission, and aneurysmal etiology.

Results:

79 consecutive SAH patients were enrolled (mean age: 54 [SD=13], 50 [63%] women, and 53 [67%] aneurysmal). 13/79 (16%) had Hunt & Hess >3. 20/79 (25%) had IOH, and 11/20 (55%) had a poor outcome vs. 19/59 (32%) without IOH (p=0.07). Median ICU LOS was longer for patients with IOH (18 vs. 11 days, p=0.01). Multivariable logistic regression found that male sex, higher APACHE II, and aneurysmal etiology, but not IOH (OR=1.1, 95% CI=0.2-5.5), were associated with poor outcome. Cox modeling did not support a significant association between IOH and ICU LOS (median increased LOS: 4-5 days; p=0.13), although male sex, aneurysmal etiology, and higher Hunt & Hess and APACHE II were associated with longer ICU LOS.

Conclusions:

IOH is associated with markers of disease severity in patients with SAH, but does not appear to add prognostic information beyond that of known risk factors. Routine ophthalmologic examination for SAH in the ICU appears unwarranted and can be deferred until the patient is stable or has visual complaints.

References:

1. Sung, Arnaldo, Sergio, Juliana, & Michel. Terson's syndrome as a prognostic factor for mortality of spontaneous subarachnoid haemorrhage. Acta Ophthalmologica 89:544-7, 2011.
2. Stienen, Lücke, Gautschi, & Harders. Terson haemorrhage in patients suffering aneurysmal subarachnoid haemorrhage: A prospective analysis of 60 consecutive patients. Clinical Neurology and Neurosurgery 114:535-8, 2012.
3. Czorlich, Skevas, Knospe, Vettorazzi, Richard, et al. Terson syndrome in subarachnoid hemorrhage, intracerebral hemorrhage, and traumatic brain injury. Neurosurgical Review 38:129-36, 2015.

Keywords: High Intracranial Pressure/Headache, Neuro-Ophth & Systemic Disease, Retina, Stroke, Vascular Disorders

Financial Disclosures: The authors had no disclosures.

Grant Support: This work was supported in part by an unrestricted departmental grant (Department of Ophthalmology) from Research to Prevent Blindness, Inc., New York. Mr. Garza receives research support from the Emory Eye Center Research to Prevent Blindness Pilot Grant and from the NIH/NCATS (TL1-TR000456-08) via the Atlanta Clinical and Translational Science Institute (ACTSI). Dr. Bruce receives research support from the NIH/NINDS (R01-NS089694).

Tuesday, March 1, 7:45 - 8:00 am
Neuroprotective Effects of ST266 in Experimental Optic Neuritis

Kenneth S. Shindler[1], Reas S Khan[1], Kimberly Dine[1], Larry Brown[2]

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Introduction:
Optic neuritis, demyelinating optic nerve inflammation, often occurs in multiple sclerosis (MS) patients. Loss of retinal ganglion cells (RGCs) and their axons also occurs in optic neuritis, and correlates with permanent vision loss. ST266 is a novel biologic mixture of growth factors and cytokines secreted from Amnion-derived Multipotent Progenitor (AMP) cells, that exhibits anti-inflammatory and neuroprotective properties in a variety of disease models. The ability of ST266 to suppress optic neuritis in the EAE model of MS was examined.

Methods:
C57/BL6 EAE mice, induced by immunization with myelin oligodendroglial glycoprotein peptide, were treated daily with one drop (6uL) of ST266 intranasally beginning before or after onset of optic neuritis. Visual function was assessed by optokinetic responses (OKR) at baseline, then weekly until sacrifice 6 weeks post-immunization. Retinas and optic nerves were isolated. RGCs were immunolabeled with Brn3a and counted. Inflammation, demyelination and axonal loss were quantified by staining of optic nerve sections.

Results:
Progressive decreases in OKR occurred in vehicle-treated EAE mice, along with significant RGC loss, consistent with prior studies showing onset of optic neuritis 12-15 days post-immunization. Daily intranasal ST266 treatment beginning on day 0 (day of immunization), 15, 22, or 30, significantly reduced the level of vision loss, and treatment from day 0 or day 15 attenuated RGC loss. ST266 also decreased the degree of demyelination and axonal loss, and reduced inflammation, in the optic nerve.

Conclusions:
ST266 treatment attenuates RGC loss, preserves OKR responses, and reduces demyelination and axonal loss during experimental optic neuritis. ST266 exerts effects with treatment initiated before and after disease onset, suggesting it may be useful as a preventative or abortive therapy. Results suggest ST266 is a potential treatment for optic neuritis that warrants further study. Furthermore, potent effects seen after intranasal administration suggest this may be a novel drug delivery method for optic neuritis.

References: None.

Keywords: Optic Neuritis, Neuroprotection, Retinal Ganglion Cell, Multiple Sclerosis

Financial Disclosures: KS Shindler has received payment for serving on the scientific advisory board for Stemnion, Inc, who produces the ST266 drug used in these studies.L Brown is employed full time by Stemnion.Stemnion provided the ST266 drug for these studies.

Grant Support: NIH Grant EY019014 Research to Prevent Blindness and the F. M. Kirby Foundation.

Tuesday, March 1, 8:00 - 8:15 am

Change in Peripapillary Bruch's Membrane Shape Can Be Detected 1 Hour After Lowering of Intracranial Pressure by Lumbar Puncture

Amulya Gampa[1], Gautam Vangipuram[2], Zainab Shirazi[1], Heather E. Moss[1,3]

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Introduction:
While papilledema is an indicator of increased intracranial pressure(ICP) in patients with idiopathic intracranial hypertension(IIH), it takes several days to develop and resolve and does not correlate with immediate changes in ICP. Prior studies have shown that there is a change in the shape of peripapillary Bruch's membrane opening (pBMO) in patients with papilledema weeks after ICP-lowering interventions. The objective of this study was to determine whether change in pBMO shape can be detected in patients with and without IIH within one hour after ICP lowering by lumbar puncture (LP).

Methods:
30 degree nasal-temporal ocular coherence tomography(OCT) B-scans were obtained within one hour before and after LP in in 34 eyes from 18 patients(age 23-86, 83% female, ICP[opening pressure] 10-55 cm H2O). pBMO shape was defined on each image using 16 equidistant points. Geometric morphometric analysis was used to identify shape-defining features (principal components [PCs]) in the image set. Generalized estimating equation models, accounting for within-subject correlations, were used to identify PCs that were associated with chronic ICP (comparing pre-LP images between eyes) and/or acute ICP changes (comparing pre- and post-LP images within eyes).

Results:
PCs 1,2,3 and 4 accounted for 76%, 18%, 2% and 2% of the pBMO shape variations, respectively. PC 1 magnitude on pre-LP images was associated with ICP ($p<0.0005$). PC 3 and 4 magnitudes changed within eyes after LP ($p = 0.034$, $p=0.049$). For each of PCs 1, 3, and 4, lower ICP corresponded with a more posterior position of the pBMO.

Conclusions:
Our geometric morphometric analysis confirms an association between pBMO shape and chronic ICP. Furthermore, we demonstrate consistent changes in pBMO shape within 1 hour of lowering ICP. This suggests that pBMO shape may be a useful marker for acute ICP changes. Further study is needed to determine how pBMO shape changes relate to clinical markers of papilledema.

References:
1. Sibony, Kupersmith, Honkanen, Rohlf, Torab-Parhiz. Effects of lowering cerebrospinal fluid pressure on the shape of the peripapillary retina in intracranial hypertension. Investigative Ophthalmology and Visual Science, 2014; 55:8223-8231.
2. Sibony, Kupersmith, Rohlf. Shape analysis of the peripapillary RPE layer in papilledema and ischemic optic neuropathy. Investigative Ophthalmology and Visual Science, 2011; 52:7987-7995.

Keywords: IIH, Papilledema, ICP, OCT

Financial Disclosures: The authors had no disclosures.

Grant Support: Sybil B. Harrington Award from Research to Prevent Blindness, NIH grant P30 EY01792, NIH grant K23 EY024345, Illinois Society for Prevention of Blindness Research Grant.

Tuesday, March 1, 8:15 - 8:30 am

Demographic, Systemic and Ocular Features of Non-Arteritic Anterior Ischemic Optic Neuropathy in a Large US Claims Beneficiary Database

Dean M. Cestari[1], Peggy Bouzika[1], Joseph F Rizzo[1], Lindsey Delott[3], Louis R Pasquale[2], Joshua D Stein[4]

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Introduction:
The etiology of non-arteritic ischemic optic neuropathy (NAION), the most common acute neuropathy in older adults, is poorly understood. We assessed demographic, systemic and ocular factors associated with NAION to gain insight into the pathogenesis of the disease.

Methods:
Claims data in a nationwide managed care network between 2001-2014 were examined for beneficiaries between the ages of 40-75 years with no history of NAION to identify new cases of NAION. All subjects were under ophthalmic surveillance and were required to have a confirmatory code for NAION in at least one subsequent visit. Multivariable Cox regression modeling was used to generate adjusted Hazard Ratios (HR) and 95% confidence intervals (CI) to assess the relation between demographic, systemic and ocular features, and the risk of developing NAION.

Results:
There were 1,381,477 eligible enrollees, 0.1% (N=977) of whom were diagnosed with NAION. Mean age ± SD for NAION at index date was 64.0±9.2 years versus 58.4±9.4 years for other beneficiaries. After adjustment for confounding factors, each additional year older was associated with a 2% increased risk of NAION (HR=1.02,95% CI:1.01-1.03). Females were 36% less likely than males to develop NAION (HR=0.64,CI:0.55-0.74). Compared with Caucasians, Latinos had a 46% decreased hazard of developing NAION (HR=0.54,CI:0.36-0.82), while African ancestry was not related to NAION (HR=0.91;95%CI:0.72-1.15). Systemic features associated with NAION included systemic hypertension (HR=1.62;95%CI:1.26-2.07) and hypercoagulable states (HR=2.46;95%CI:1.51-4.00). Diabetes was not associated with NAION, unless there was end organ involvement, which produced a 27% increased hazard of NAION (HR=1.27;95%CI:1.01-1.59). Ocular features associated with NAION were age-related macular degeneration (HR=1.29;95%CI:1.08-1.54) and retinal vein occlusion (HR=3.94;9%CI:3.11-4.99).

Conclusions:
This is the first large scale population survey of NAION. This study revealed gender, race and systemic disease factors that influence the risk of developing NAION. This data can motivate new investigations to explore the pathogenesis of NAION.

References: None.

Keywords: NAION, Risk Factors, Optic Neuropathy, Patient Database

Financial Disclosures: The authors had no disclosures.

Grant Support: Joshua D. Stein, MD MS has support from an RPB (Physician Scientist Award).

Tuesday, March 1, 8:30 - 8:45 am
The Effect of Pupillary Dilation on Strabismus Measurements in Adults

Michael S. Lee[1], Erick Bothun, Kimberly Merrill, Anna Schweigert, Andrea Kramer, Katherine Hogue, Jill Anderson, Sean Rivera

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Introduction:
Pupillary dilation can significantly alter strabismus measurements in pediatric patients. This study aims to determine if pupillary dilation affects strabismus measurements in adults.

Methods:
Patients aged 18 years and older with strabismus were eligible. Each underwent standard evaluation of motility, stereopsis, and ocular alignment with alternate prism cover test by a certified orthoptist. After pupillary dilation with phenylephrine 2.5% and tropicamide 1%, ocular alignment was re-measured in primary gaze at 6 m and 1/3m (with and without +3.00 lens) by a second, masked orthoptist.

Results:
Fifty-six patients (59% women, age range: 19-92, mean age: 51.6 years) were enrolled with the following deviations in primary gaze before dilation: esodeviation (n=14, range 1-52, mean 15.7 PD), exodeviation (n=4, range 2-20, mean 10.9 PD), mixed vertical/esodeviation (n=11, ET: range 2-45, mean 13.1 PD; HT: range 1-25, mean 6.4 PD), mixed vertical/exodeviation (n= 14, XT: range 2-55, mean 16.6 PD; HT: range 2-10, mean 5.3 PD), vertical deviation (n=13, range 1-20, mean 5.7 PD). For horizontal misalignments, the mean change in PD after dilation was 1.65 at distance (95% CI +/- 0.77, p=0.99), 4.33 at near (95% CI +/- 1.47, p=0.77), and 3.51 at near with +3.00 add (95% CI +/- 1.17, p=0.95). For vertical measurements the change was 0.76 at distance (95% CI +/- 0.31, p=0.99), 1.33 at near (95% CI +/- 0.53, p=0.99), and 1.16 at near with +3.00 (95% CI +/- 0.67, p=0.99). Significant change was observed in those aged 18-39 (mean 9.59, 95%CI +/-3.90, p=0.0023), but not after +3.00 add was used (mean 4.41, 95%CI +/- 5.75, p=0.64).

Conclusions:
Pupil dilation does not affect distance strabismus measurements in adults. Measurements at near are significantly different in non-presbyopic adults, but this can be mitigated by +3.00 lenses.

References: None.

Keywords: Strabismus, Dilation, Pupil

Financial Disclosures: The authors had no disclosures.

Grant Support: Research to Prevent Blindness, New York, NY.

Tuesday, March 1, 8:45 - 9:00 am
Wilbrand's Knee Revisited

Jaydeep Kachhela[1], Cha-Min Tang[1], Robert K. Shin[2]

[1]University of Maryland/Department of Neurology, Baltimore, MD, USA, [2]Georgetown University/Department of Neurology, Washington, DC, USA

Introduction:
Over a century ago, German ophthalmologist Hermann Wilbrand studied human optic chiasms and reported that inferonasal crossing fibers within the chiasm curved anteriorly into the contralateral optic nerve. This anatomic bend ("Wilbrand's knee") is classically cited as the explanation for the contralateral superotemporal visual field defect that may appear when a lesion affects the optic nerve at its junction with the chiasm (the so-called "junctional scotoma"). More recent reports have called into question the existence of Wilbrand's knee or suggested that it may simply be an artifact of monocular enucleation, partly because no evidence of Wilbrand's knee could be found in monkey optic chiasms.

Methods:
Four human optic chiasms (obtained from cadaver donors with normal pre-mortem vision) and three monkey chiasms were fixed and thin sectioned (40 µm), then examined using a novel imaging technology that takes advantage of the observation that light will reflect/scatter off of well-defined linear structures (i.e., axons) in a predictable manner based on their orientation. Using this technique, tissue structures oriented in different directions can be clearly distinguished, allowing tractography similar to DTI MRI but with a 10- to 100-fold higher resolution.

Results:
In all four human optic chiasms (three axial sections and one coronal section), thin fiber tracts consistent with those Wilbrand had described were observed. No such tracts were found in the three monkey chiasms (two axial sections and one coronal section).

Conclusions:
Wilbrand's knee exists in humans but is not present in monkeys, which may explain conflicting reports in the literature regarding its existence.

References:
1. Wilbrand H, Saenger A. Die Neurologie des Auges. Wiesbaden, J Bergmann, vol 3, pp 98-120, 1904.
2. Wilbrand H, Saenger A. Die Neurologie des Auges. Wiesbaden, J Bergmann, vol 6, pp 15-17, 1915.
3. Horton JC. Wilbrand's knee of the primate optic chiasm is an artefact of mononuclear enucleation. Trans Am Ophthalmol Soc., vol 95, pp 579-609, 1997.
4. Lee JH, Tobias S, Kwon JT, Sade B, Kosmorsky G. Wilbrand's knee: does it exist? Surg Neurol., vol 66, pp 11-17, 2006.
5. Shin RK, Qureshi RA, Harris NR, et al. Wilbrand knee. Neurology, vol 82, pp 459-460, 2014.

Keywords: Neuroimaging, Visual Fields

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Tuesday, March 1, 9:00 - 9:15 am

Cranio-Spinal CSF Redistribution Before and Following Lumbar Puncture in Patients with Idiopathic Intracranial Hypertension

Byron L. Lam[1], Noam Alperin[2], Jennifer Verriotto[1], Joshua Pasol[1], Bahareh Hassanzadeh[1], Sean Gratton[1], Sang H. Lee[2], Ahmet M. Bagci[2]

[1]University of Miami, Bascom Palmer Eye Institute, Miami, FL, USA, [2]University of Miami, Radiology, Miami, FL, USA

Introduction:

The physiologic effect of lumbar puncture (LP) in idiopathic intracranial hypertension (IIH) has not been adequately studied and automated quantitation of cerebrospinal fluid (CSF) volumes by MRI is lacking. We characterized the physiologic effect of LP by determining the change of cranio-spinal CSF redistribution before and after LP. To achieve this aim, we developed a new automated method for delineating spinal CSF spaces.

Methods:

The study subjects consists of 8 young overweight women with newly-diagnosed untreated IIH (Age 29±5.9 years, BMI 34±6.7). Research cranio-spinal MRIs were performed immediately before and immediately after the diagnostic LP to establish IIH (opening pressure 33±9.1 cm water). MR imaging included T1W MPRAGE and T2W SPACE sequences of the brain and 2 separate T2W SPACE sequences covering the upper and lower portions of the spinal canal. Cranio-spinal CSF volumes prior and following LP were compared to the amount of CSF withdrawn.

Results:

LP results in reduced spinal CSF volume localized near the region of the LP without change in cranial CSF volume. Spinal CSF and cord volumetric automated measurements were highly reproducible with mean variability of less than 1%, -0.7±1.4%, -0.7±1.0%, respectively. The pre-to-post CSF withdrawal differences in the cranio-spinal CSF volumes were consistently smaller and strongly correlated with the CSF amounts removed (R=0.86,p=0.006). The smaller measured pre-to-post LP CSF differences compared to the CSF amount withdrawn can be reconciled assuming a net CSF formation of 0.41±0.18ml/min.

Conclusions:

Despite the high intracranial pressure, the drop in intracranial pressure from LP in IIH is related to the immediate increase in spinal canal compliance from CSF removal near the spinal region of the LP without change in cranial CSF volume. Our findings enhance the understanding of the CSF flow dynamics of LP in IIH, and the automated method developed permit future longitudinal studies to assess cranio-spinal CSF in IIH patients.

References: None.

Keywords: Idiopathic Intracranial Hypertension, Lumbar Puncture, Cerebral Spinal Fluid, MRI

Financial Disclosures: The authors had no disclosures.

Grant Support: Funded by NANOS pilot grant.

Tuesday, March 1, 10:00 - 10:15 am

Glucagon Like Peptide-1 (GLP-1) Reduces Cerebrospinal Fluid Secretion and Intracranial Pressure: A Novel Treatment for Idiopathic Intracranial Hypertension?

Alexandra Sinclair[1,2], Maria Uldall[3], James Mitchell[1], Ana Maria Gonzalez[1], Rigmor Jensen[3], Hannah Botfield[1]

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Introduction:
Introduction: To investigate whether the gut neuropeptide, Exendin-4, a glucagon like peptide-1 (GLP-1) receptor agonist (currently used to treat diabetes and obesity), would be able to modulate CSF secretion at the choroid plexus and subsequently reduce ICP.

Methods:
Methods: GLP-1 receptor mRNA, protein levels and localisation were assessed by quantitative PCR, western blot and immunohistochemistry respectively, with and without Exendin-4 treatment. Activation of the receptor was evaluated using a cAMP immunoassay and $Na^+ K^+$ ATPase activity was measured to assess CSF secretion. The effect of Exendin-4 on ICP was assessed in adult rats.

Results:
Results: We demonstrated that GLP-1 receptor mRNA and protein were detected in the choroid plexus and was localised to the cytoplasm and apical surface of the epithelial cells. Following Exendin-4 treatment, GLP-1 receptor mRNA (3.40±0.78 fold, $P<0.05$) and protein levels (0.92±0.05, $P<0.05$) were increased compared to baseline (1.00±0.20 fold and 0.59±0.06 respectively). Evaluation of the downstream signalling pathway on primary choroid plexus epithelial cells identified a 2.14±0.61 fold increase in cAMP after Exendin-4 treatment ($P<0.01$). Exendin-4 also significantly reduced $Na^+ K^+$ ATPase activity, a marker of CSF secretion (39.3±9.4% of control; $P<0.05$). Finally, *in vivo* ICP recording in adult rats demonstrated that Exendin-4 significantly reduced ICP (41.7±5.0% reduction from baseline $P<0.0001$).

Conclusions:
Conclusions: We demonstrate that Exendin-4 reduces CSF secretion by the choroid plexus and ICP in rats. Repurposing existing GLP-1 drugs may represent a novel therapeutic strategy for conditions of raised ICP such as idiopathic intracranial hypertension. Additionally, GLP-1 therapy promotes significant weight loss which would be advantageous in idiopathic intracranial hypertension.

References: None.

Keywords: Idiopathic Intracranial Hypertension, Glucagon Like Peptide 1, Intracranial Pressure, Choroid Plexus, Cerebrospinal Fluid Secretion

Financial Disclosures: The authors had no disclosures.

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Tuesday, March 1, 10:15 - 10:30 am

Recombinant AAV2 Containing the Wild-Type *ND4* Gene (rAAV2/2-*ND4*) is an Experimental Gene Therapy for Vision Loss in LHON Due to the *ND4* Mitochondrial Mutation: Phase I/IIa Safety Investigation Results and Upcoming Pivotal Phase III Efficacy Studies

Catherine Vignal[1,2], Scott Uretsky[3], Nitza Thomasson[3], Geraldine Honnet[4], Marisol Corral-Debrinski[5], Celine Bouquet[3], Anne Galy[3], Jean-Philippe Combal[3], Serge Fitoussi[3], José A. Sahel[1,2,6]

[1]Centre Hospitalier National d'Ophtalmologie des Quinze-Vingts, Paris, France, [2]Fondation Ophtalmologique A de Rothschild, Paris, France, [3]Gensight-Biologics, Paris, France, [4]Genethon, Evry, France, [5]Inserm UMR 1141, Paris, France, [6]Institut de la Vision, Paris, France

Introduction:
Allotopic expression of the wild-type ND4 gene delivered by a rAAV2/2 vector through intra-vitreal injection is an experimental therapy for vision loss in patients with ND4 LHON.

Methods:
An open-label Phase I/IIa safety study included patients with vision loss due to ND4 LHON. Four dose escalation cohorts and an extension cohort were comprised of 3 patients each. Patients received a single intra-vitreal injection of rAAV2/2-ND4 in their worse seeing eye. Primary outcome was the occurrence of adverse events (AE). Secondary outcomes included immune response to AAV2 and evaluation of visual function

Results:
Fifteen patients were included. Average duration of vision loss was 5.9 years (0.62-22.2) at treatment. Mean LogMAR acuity of the injected eye at study entry was 2.25 (1.10-3.01). Follow-up includes the 2 week visit of the extension (last) cohort. Thirteen of 15 patients experienced an AE. A total of 57 AEs were documented; 24 considered related to GS010 and 13 considered related to procedures. No GS010-related, unexpected AE occurred. One serious AE unrelated to GS010 or procedures occurred. The most common ocular AEs were inflammation and IOP elevation. All AEs were mild except 2 moderate IOP elevations and one severe event each of anterior chamber and vitreous inflammation. Ocular side effects are improving or resolved with standard therapy and no visual sequelae occurred. Typical immune responses to AAV2 were observed and no relationship between anti-AAV2 antibody levels (IgG, neutralizing antibodies) and ocular inflammation was noted. At 24 weeks post-injection some patients were noted to have a trend of effect on visual acuity, color vision and contrast sensitivity in the treated eye.

Conclusions:
Intra-vitreal injection of rAAV2/2-ND4 is safe and encouraging trends on vision testing are noted. Dose selection is completed for the pivotal Phase III trials RESCUE and REVERSE which will include patients with vision loss up for to 1 year

References: None.

Keywords: Optic Neuropathy, Genetic Disease

Financial Disclosures: C Vignal consultant for Gensight-Biologics S Uretsky, N Thomasson, A Gay, JP Combal, S Fitoussi : Gensight-Biologics employees JA Sahel Gensight-Biologics Share Holder and Consultant

Grant Support: None.

Tuesday, March 1, 10:30 - 10:45 am

Light Evoked Retinal Activation is Metabolically Coupled to Increases in Human Retinal, Choroidal and Optic Nerve Head Blood Flow Measured Simultaneously by Laser Speckle Flowgraphy

Ruben Torres-Torres[1], Pieter Poolman[2,3], Randy Kardon[2,3]

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Introduction:
Our purpose was to develop a light-induced metabolic stress test for use in disorders of the retina and optic nerve. The direct relationship between neural activation and blood flow is well known and forms the basis for quantitative, functional imaging of the brain. Neurovascular coupling to light stimuli has also been described for the retinal vasculature. Laser speckle flowgraphy provides a means to quantify light-induced changes in retinal, choroidal, and optic nerve head circulations simultaneously throughout the cardiac cycle.

Methods:
10 healthy subjects (mean age 39; range 18 to 61 years old; 4 males and 6 females) were studied using laser speckle flowgraphy (LSFG-NAVI device, Softcare Co. LTC, Fukuoka, Japan). After two baseline blood flow measurements were made, a 10Hz flickering light stimulus with 50% duty cycle and145,96 cd/m2 of luminance was given using a portable, wireless LED array, while recording blood flow. The white light-induced blood flow response of the right eye was measured in the first experiment while the consensual blood flow response of the left eye was recorded in the second experiment. Blood pressure and intraocular pressure were measured before, during and after each 30-second light stimulus.

Results:
A significant increase in flicker-induced blood flow was found in the stimulated eye in 3 vascular beds simultaneously measured: retina; 35.3%±6.5, choroid; 16.1%±3.3, and optic nerve head; 12.5%±4.8. The consensual effect was significantly lower in the non-stimulated eye and was mainly explained by an increase in systemic blood pressure.

Conclusions:
Our results show that the retina, choroid, and optic nerve head adjust their blood flow to the metabolic demands in a coordinated way, and the lack of response in the non-stimulated eye suggests a local response. Laser speckle flowgraphy measurement of light-induced neurovascular coupling has potential for use as a metabolic stress test of the retina and optic nerve in health and disease.

References: None.

Keywords: Neurovascular Coupling, Laser Speckle, Optic Nerve Flow, Retinal Blood Flow, Choroidal Blood Flow

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Tuesday, March 1, 10:45 - 11:00 am

A Novel Approach to Measuring Peripapillary Retinal Perfusion in Papilledema: A Pilot Study Using Optical Coherence Tomography Angiography

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Introduction:

The utility of Optical Coherence Tomography Angiography (OCTA) in imaging perfused radial peripapillary capillaries (RPCs) has been demonstrated.[1] The purpose of this pilot study was to assess the density of perfused RPCs in subjects with papilledema and normals.

Methods:

Subjects were prospectively recruited from a single institution. Peripapillary 4.5x4.5mm scans were obtained in each subject using a 70-kHz, 840nm wavelength spectral OCT system (Avanti RTVue-XR, Optovue, Fremont, CA). The split-spectrum amplitude decorrelation angiography (SSADA) algorithm was used to identify perfused RPCs. A customized algorithm was applied to perform vessel skeletonization and generate a color-coded capillary perfusion density (CPD) map. The algorithm also calculated mean whole en face and peripapillary CPD within a 0.75 mm width ring surrounding the nerve. We performed qualitative analysis of CPD maps and quantitative analysis of whole en face and peripapillary CPD values in papilledema and normal patients. Statistical analysis was performed using a two-tailed student t-test.

Results:

Images from 13 subjects with papilledema and 13 normals were included. Qualitative analysis of whole en face CPD maps revealed dense RPC networks in normals, and patchy areas of decreased capillary density in papilledema subjects. Quantitative analysis of whole en face CPD was not statistically significant. In contrast, mean peripapillary CPD values were decreased in papilledema (59.1%) compared to normals (63.1%). (P=0.001). Subgroup analysis of Frisén[2] low (0-II) and high (III-V) grade papilledema revealed decreases of 5.9% (P<0.01) and 8.1% (P=0.01), respectively, compared to normals.

Conclusions:

Mean peripapillary CPD was decreased in papilledema subjects compared to normals, as measured by OCTA. This finding may suggest reduced flow from vascular congestion at the peripapillary region. These vascular changes may be useful in the understanding of structural and functional relationships in papilledema.

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Keywords: OCT Angiography, Ocular Imaging, Papilledema, Retinal Perfusion, IIH

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Tuesday, March 1, 11:00 - 11:15 am
The Effect of Red Light Exposure on the Pre-existing Melanopsin-Driven Post-illumination Pupil Response

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Introduction:
Intrinsically photosensitive retinal ganglion cells (ipRGCs), the specific sub-group of retinal ganglion cells that mediate the pupillary light reflex, contain a bistable photo-pigment called melanopsin. The activation of melanopsin drives a persistent firing of ipRGCs resulting in a sustained pupil constriction after the offset of light stimulation (post-illumination pupil response, PIPR). It has been proposed that after activation by blue light, activated melanopsin is converted back to its resting state by long wavelength light exposure, a putative mechanism of melanopsin chromophore recovery in vivo. We tested this hypothesis by investigating whether red light attenuates the ongoing post-illumination pupil response (PIPR) induced by melanopsin-activating blue light.

Methods:
Pupillary light responses were tested using “Blue + Red” double flashes and “Blue only” single flash stimuli in 10 visually normal subjects (mean age 31.8 years, range 20-57 years). For “Blue + Red” conditions, PIPR was induced with an intense blue flash, immediately followed by experimental red light exposure of variable intensity and duration (Experiment 1) or 9 s after the offset of the blue flash (Experiment 2). For “Blue only” conditions, only the PIPR-inducing blue stimuli were presented (reference condition). PIPR was defined as the mean pupil size from 10 to 30 seconds (Experiment 1) or 25 to 60 seconds (Experiment 2) after the offset of blue light stimuli.

Results:
PIPR from “Blue + Red” conditions did not differ significantly from those of “Blue only” conditions ($p=0.551$) in Experiment 1. They also did not differ in Experiment 2 ($p= 0.413$).

Conclusions:
Red light exposure does not alter the trajectory of PIPR induced by blue light. This finding does not support the hypothesis that long wavelength light reverses activated melanopsin; rather it lends support to the hypothesis that the spectral distributions of stimuli driving the forward and backward reactions of melanopsin may be similar.

References: None.

Keywords: Pupil Light Reflex, Chromatic Pupillometry, Melanopsin, Post-Illumination Pupil Response

Financial Disclosures: The authors had no disclosures.

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Tuesday, March 1, 11:15 - 11:30 am

Experimental Anterior Ischemic Optic Neuropathy in Diabetic Mice Exhibited Severe Retinal Swelling and Subretinal Fluid Accumulation Acutely and More Severe Thinning Chronically

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Introduction:

Non-arteritic ischemic optic neuropathy (AION) is the most common acute optic neuropathy in those older than 50[1-2] and is associated with post-ischemic inflammation and oligodendrocyte dysfunction and degeneration.[3-8] Diabetes mellitus (DM) is one of the most common vascular risk factors and leads to vascular changes, inflammation, and neuron loss.[7] We studied the contribution of elevated glucose in experimental AION and assessed retinal and inflammatory changes.

Methods:

We induced photochemical thrombosis model of AION[3-8] in STZ-induced chronically diabetic C57BL/6 mice (N = 43) and performed optical coherence tomography (OCT), fluorescence angiography (FA), and immunohistochemical and morphometric analyses of anti-Iba-1 antibody stain (activated microglia). Statistical analysis was performed using SPSS.

Results:

We measured post-ischemic swelling one-day after AION using OCT and found there was significant swelling of the ganglion cell complex (GCC: RNFL+GCL+IPL) and increased total retinal thickness ($P < 0.01$) in animals with or without DM, which was associated with increased Iba-1$^+$ staining at the optic nerve head and microglial activation. There was more subretinal fluid accumulation in the DM-AION eyes compared with non-DM AION eyes, and the subretinal fluid was more prominent further away from the optic nerve head. In the DM mice, there was no correlation between serum glucose level and the severity of swelling. There was greater GCC thinning in DM mice at week-1 (DM: 79.2 ± 1.2 µm, non-DM: 97.6 ± 11.2 µm, $P = 0.096$) and at week-4 (DM: 66.6 ± 2.9 µm, non-DM: 74.7 ± 3.5 µm, $P = 0.2$).

Conclusions:

After AION, there was post-ischemic inflammation and microglial activation, which was similar in diabetic- and non-diabetic mice, but diabetes was associated with greater swelling and subretinal fluid one day after ischemia and greater thinning four weeks later.

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Keywords: Optic Neuropathy (AION), Diagnositic Tests (OCT)

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Tuesday, March 1, 11:30 - 11:45 am

Change in the Deflection of the Neural Canal Opening Away from the Vitreous and Towards the Retrobulbar Space as an Indicator of Treatment Efficacy of Optic Nerve Sheath Fenestration and Non-surgical Treatment for Idiopathic Intracranial Hypertension (IIH)

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Introduction:
Our purpose was to determine if change in the displacement of Bruch's basement membrane (BM) surrounding the neural canal of the optic disc could reveal surgical and medical treatment efficacy of IIH. We also sought to determine if BM displacement was independent of reductions in optic nerve volume.

Methods:
The displacement of Bruch's membrane surrounding the neural canal of the optic disc was quantified from OCT scans of the optic disc using shape analysis before and after treatment of papilledema. 39 patients treated with maximum tolerated acetazolamide+diet (ACZ+diet) were compared to 34 patients treated with placebo+diet (PL+diet) from the OCT substudy of the Idiopathic Intracranial Hypertension Treatment Trial (IIHTT). 6 patients not enrolled in the IIHTT were treated with optic nerve sheath fenestration (ONSF). The 2nd principal component coefficient from the shape analysis reflected the BM anterior/posterior displacement; more negative values reflected anterior displacement towards the vitreous and more positive values reflecting a posterior displacement away from the vitreous (-3.0 to +3.0). Disc volume was determined by segmentation analysis of the OCT disc volume scan.

Results:
There was a statistically significant posterior deformation of Bruch's membrane layer after treatment for both the ACZ+diet group (+0.87±1.2) and the eye receiving ONSF (+1.59±1.5). There was no significant change in displacement of BM in either the PL+diet group (+0.03±.83) or the fellow eye not receiving ONSF (+.14±1.0). Disc volume decreased significantly in all groups.

Conclusions:
Displacement of Bruch's membrane at the optic nerve head reflects the translaminar pressure differential between the retrolaminar and intraocular fluid compartments and appears to be a biomarker of successful treatment of raised intracranial pressure. Unexpectedly, reduction in disc volume did not correlate with BM displacement, implying two independent mechanisms for improvement.

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Keywords: IIH, OCT, Neural Canal, Optic Nerve Sheath Fenestration, Papilledema

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Tuesday, March 1, 11:45 am - 12:00 pm
The Localization and Patterns of Dyschromatopsia: A Study of Prosopagnosic Subjects

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Introduction:
Dyschromatopsia can accompany acquired prosopagnosia, but given the structural variety of the latter, it is not clear which lesions are associated with colour impairments, or whether these impairments also occur with developmental prosopagnosia. In addition, whether the impairment selectively affects specific regions of colour space is uncertain, given conflicting reports in prior single cases.

Methods:
We investigated hue discrimination in a cohort of 12 subjects with acquired prosopagnosia and 9 with developmental prosopagnosia, along with 42 matched controls, using the Farnsworth-Munsell 100-hue test. Behavioural results were subjected to a Fourier analysis, and neuroimaging to a lesion overlap analysis.

Results:
We found impaired hue discrimination in 6 subjects with acquired prosopagnosia, 5 with bilateral and one with a unilateral occipitotemporal lesion. Structural MRI analysis showed maximum overlap of lesions in the right and left lingual and fusiform gyri. Fourier analysis of their error scores showed tritanopic-like deficits and blue-green impairments, similar to tendencies displayed by the healthy controls. Three subjects also showed a novel fourth Fourier component, indicating additional peak deficits in purple and green-yellow regions. No subject with developmental prosopagnosia had impaired hue discrimination.

Conclusions:
In subjects with prosopagnosia, dyschromatopsia is limited to those with acquired lesions of the fusiform gyri, usually bilateral but sometimes unilateral. The dyschromatopsic deficit shows an accentuation of normal tritatanopic-like tendencies, sometimes accompanied by anomalous deficits that do not correspond to traditional red-green axes.

References: None.

Keywords: Hue Discrimination, Face Recognition, Prosopagnosia, Fusiform Gyrus

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