PLATFORM SESSION I
Monday, February 23, 2015 • 5:00 p.m. - 7:00 p.m.

Moderators: Laura Balcer, MD, MSCE & Beau Bruce, MD

5:00 p.m. - 5:15 p.m.
Bo Young Chun
Lipocalin-2 Expression in Demyelinating Optic Neuritis of Experimental Autoimmune Encephalomyelitis Model and Their Pivotal Role

5:15 p.m. - 5:30 p.m.
Catherine Vignal
Preliminary Safety and Tolerability Results of a Recombinant Adeno-Associated Viral Vector Serotype 2 (Raav2/2) Containing the Human Wild-Type Mitochondrial NADH Dehydrogenase 4 (ND4) Gene, in Patients with Leber Hereditary Optic Neuropathy Due to the G11778A Mitochondrial DNA Mutation

5:30 p.m. - 5:45 p.m.
Eric D. Gaier
Clinical Features of OPA1-Related Optic Neuropathy: A Focus on Genetic Modifiers

5:45 p.m. - 6:00 p.m.
Brian R. Younge
Cytokine Mechanisms in Giant Cell Arteritis

6:00 p.m. - 6:15 p.m.
Umur A. Kayabasi
Retina Examination with Curcumin for Tau Tangles and Beta Amyloid in Alzheimer's Disease

6:15 p.m. - 6:30 p.m.
Samuel Bidot
Role of The Optic Canal Size On The Severity Of Papilledema And Visual Outcome In Idiopathic Intracranial Hypertension (IIH)

6:30 p.m. - 6:45 p.m.
Randy H. Kardon
A New Pupil Light Reflex Test for Detecting Optic Neuropathy Independent of the Fellow Eye Which Highly Correlates to Visual Field Volume

6:45 p.m. - 7:00 p.m.
Neda Anssari
Color Vision Deficits in Multiple Sclerosis
Monday, February 23, 5:00 - 5:15 p.m.

Lipocalin-2 Expression in Demyelinating Optic Neuritis of Experimental Autoimmune Encephalomyelitis Model and their Pivotal Role

Bo Young Chun¹, Jong-Heon Kim², Youngpyo Nam², Seungwoo Han³, Kyoungho Suk²

¹Department of ophthalmology, Kyungpook National University Hospital, Daegu, Korea, ²Department of Pharmacology, Brain science and engineering institute, Kyungpook National University School of Medicine, Daegu, Korea, ³Division of Rheumatology, Department of Internal Medicine, Daegu Fatima Hospital, Daegu, Korea

Introduction:
The purpose of this study is to determine the role of lipocalin 2 (LCN2) in experimental autoimmune optic neuritis (EAON) model. We compared degrees of neuro-inflammation between LCN2 knock out (KO) mice and wild type (WT) littermates by histological analysis of demyelination, reactive astrocytosis and proliferation of microglia.

Methods:
EAON was induced by subcutaneous immunization with emulsified mixture of myelin oligodendrocyte glycoprotein (MOG35-55) peptide in LCN2 KO mice and WT littermates. Mice were examined daily and scored for disease severity. At post-immunization day 17, mice were killed and their eyes were enucleated. Comparison of degrees of demyelination, activated neuroglial cells and profiling of cytokines and chemokines between LCN2 KO mice and WT littermates following EAON induction was done by immunohistochemistry and real-time PCR respectively.

Results:
EAON was well induced in WT littermates, however, LCN2 KO mice were resistant to the EAON induction. The expression of LCN2 was notably increased by reactive astrocytosis in the optic nerve of WT littermates. A remarkable reduction of demyelination and astrocytosis of the optic nerve was demonstrated in the LCN2 KO mice. Restrained microglial activation compared to WT littermates was also observed in the optic nerve of LCN2 KO mice. LCN2 KO mice showed a markedly reduced M1-related gene expression associated with an attenuated toll-like receptor signaling.

Conclusions:
In this study, the significant induction of LCN2 expression was observed in the optic nerve of the EAON mice compared to naïve mice and was mostly detected in reactive astrocytosis. These results imply that LCN2 may be a critical mediator of autoimmune inflammation in EAON.

References:
None.

Keywords: Experimental Autoimmune Optic Neuritis, Lipocalin 2, Demyelination, Reactive Astrocytosis, Microglial Activation

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Preliminary Safety and Tolerability Results Of A Recombinant Adeno-Associated Viral Vector Serotype 2 (rAAV2/2) Containing The Human Wild-Type Mitochondrial NADH Dehydrogenase 4 (ND4) Gene, In Patients With Leber Hereditary Optic Neuropathy Due To The G11778A Mitochondrial DNA Mutation

Catherine Vignal 1,2, Géraldine Honnet 3, Anne Galy 4, Nitza Thomasson 4, Marisol Corral Debrinsky 5, Scott Uretsky 4, Jean-Philippe Combal 4, Serge Fitoussi 4, Jose A. Sahel1,5

1CHNO, Paris, France, 2Fondation Rothschild, Paris, France, 3Genethon, Evry, France, 4GenSight-Biologics, Paris, France, 5Institut de la Vision, Paris, France

Introduction:
Our goal is to report the results of a first-in-man safety trial of gene therapy in patients with Leber Hereditary Optic Neuropathy (LHON).

Methods:
Two cohorts each comprised of 3 patients with the G11778A ND4 mutation and severe visual loss (≤20/200) received ascending doses of intravitreal (IVT) recombinant adeno-associated viral vector (rAAV2/2) containing the wild-type ND4 gene.

Baseline general and ophthalmic examinations, laboratory and EKG parameters were obtained. Paracentesis (6/6) and intra-ocular pressure (IOP) lowering treatment (5/6) preceded IVT. In-patient observation for 24-hours post-IVT ensued with IOP measurement at 0.5, 2, 4, and 24-hours. Follow-up visits including vital signs, IOP, ophthalmic examinations, laboratory evaluation, immune-monitoring and assessment of adverse events (AE, SAE) are conducted at 0.5, 1, 2, 4, 8, 12, 24, 36 and 48-weeks post-IVT. Bio-dissemination in blood, urine and tears were evaluated for two weeks post-IVT. The first cohort received 9E+09vg/eye. A data safety monitoring board evaluated the safety of this dose before escalation to 3E+10vg/eye in the second cohort.

Results:
8 LHON patients were screened, 6 were included (time since vision loss 7.5-254 months). No SAE or treatment-related systemic AE occurred. 5/6 patients had non-sustained, topical-treatment responsive, elevated IOP; 3/5 patients within 4-hours post-IVT and 2/5 patients at 2-weeks post-IVT [elevated IOP range: 23-34mmHg]. 3/6 patients experienced mild anterior chamber inflammation between 4 and 8 weeks post-IVT requiring topical treatment in 2/3. Visual acuity remained unchanged.

Conclusions:
Overall safety and tolerability of a single IVT injection of rAAV2/2 was good. Post-IVT IOP elevation (mechanistic) and mild ocular inflammation (pre-clinical studies) occurred as expected; both were mild and reversible with local treatment. These results allowed for dose escalation necessary to identify the highest tolerated dose of IVT-rAAV2/2 that will be used in our upcoming study of clinical efficacy in more recently affected LHON G11778A patients.

References: None.

Keywords: Leber Hereditary Optic Neuropathy, Mitochondrial Genetic Disorder, Gene Therapy, Adeno Associated Viral Vector, Safety and Tolerability Trial


Grant Support: None.
Monday, February 23, 5:30 - 5:45 p.m.

Clinical Features of OPA1-Related Optic Neuropathy: A Focus on Genetic Modifiers

Eric D Gaier1,2, Katherine Boudreault3, Isao Nakata3, Maria Janessian2, Elizabeth Delbono2,4, Simmons Lessell3,5, Dean Cestari3,5, Janey L Wiggs1,2,4,5, Joseph F Rizzo3,5

1Department of Ophthalmology, Boston, MA, USA, 2Howe Laboratory, Boston, MA, USA, 3Department of Neuro-Ophthalmology, Boston, MA, USA, 4Department of Glaucoma, Boston, MA, USA, 5Harvard Medical School, Boston, MA, USA

Introduction:
Dominant optic atrophy (DOA) is the most common hereditary optic neuropathy, and known mutations in OPA1 account for 40-60% of cases. Previous studies investigating clinical features in DOA patients with OPA1 mutations have been limited to a few mutations and few include OPA1 copy number variant (CNV) analyses or mitochondrial genomic analyses. We hypothesized that some clinical presentations depend upon both OPA1 status and the background mitochondrial haplogroup.

Methods:
This is an updated retrospective case series of 86 patients with bilateral optic atrophy referred for genetic testing at a tertiary care center using selective exon capture followed by next generation sequencing for OPA1 and the mitochondrial genome. Patients were also screened for CNVs involving OPA1 using Multiplex Ligation-dependent Probe Amplification (MLPA) analysis and array CGH (comparative genomic hybridization). Mitochondrial haplogroups were defined by mitochondrial genome analysis. Clinical features, including visual acuity, Ishihara testing, automated visual field testing and dilated funduscopy, were analyzed by OPA1 mutation and mitochondrial haplogroups.

Results:
Twenty nine cases were found to have OPA1 disease-causing mutations including 4 novel sequence mutations and 6 CNVs. OPA1-positive patients were younger at symptom onset but had less severe visual field deficits than OPA1-negative patients. Four of 21 OPA1-positive cases had mitochondrial haplogroup “J”, compared to 4/34 OPA1-negative cases. Three of those four with OPA1 mutations and haplotype “J” had extraocular neurological symptoms, consistent with a DOA+ phenotype.

Conclusions:
This is the first study to include CNV testing and mitochondrial group analyses in clinical studies of DOA. Mitochondrial haplogroup “J” may interact with OPA1 genotype affecting DOA phenotype although further study of larger datasets will be necessary to confirm this. By continuing to study the interactions between genetic and clinical features of DOA, we will expand our knowledge of DOA pathophysiology to guide diagnostic decision-making and testing of potential disease-modifying treatments.

References: None.

Keywords: Genetic Disease, Optic Neuropathy, Visual Fields

Financial Disclosures: The authors had no disclosures.

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Monday, February 23, 5:45 - 6:00 p.m.

Cytokine Mechanisms in Giant Cell Arteritis

Brian R Younge¹, Gene Hunder², Cornelia M Weyand³

¹Mayo Clinic, Rochester, MN, USA, ²Mayo Clinic, Rochester, MN, USA, ³Stanford University, Stanford, CA, USA

Introduction:
In a series of 41 patients with pathologically confirmed giant cell arteritis (GCA) cytokine studies were undertaken from both tissue and blood samples to determine T-cell mechanisms prior to and after treatment began.

Methods:
Cytokine analysis was done on both tissue and blood samples by culture and flow cytometry to determine the major mediators of inflammation and the response of the Th1 and Th17 cells to treatment. Groups of 10 patients were studied after treatment was begun at intervals of 3, 6, 9 and 12 months with repeat biopsy (the other side) and blood studies.

Results:
Pathologic reversal of inflammatory response takes 9-12 months or sometimes longer in 20 percent of the patients studied. The CD4 T cells are the primary mediators of the inflammatory response. Th1 cells that produce interferon gamma, among other cytokines and Th17 cells that produce interleukine-17 among other cytokines are markedly upregulated in active GCA. Steroids only affect the Th17 line of cells and their respective cytokines, but do not affect the Th1 cells nor their cytokines.

Conclusions:
The rapid clinical response to steroid treatment in GCA is largely explained by the sharp reduction of Th17 cells and their respective cytokines. Persistence of the disease both pathologically and biochemically for several months may be explained by the failure of Th1 cells to respond to steroids. Targeting specific cytokines in future holds promise for improved treatments that may improve the biochemical response and reduce the need for prolonged steroids.

References:

Keywords: Cytokines, Th1 Cells, Th17 Cells, Giant Cell Arteritis

Financial Disclosures: The authors had no disclosures.

Grant Support: Research to Prevent Blindness
Monday, February 23, 6:00 - 6:15 p.m.

Retina Examination with Curcumin for Tau Tangles and Beta Amyloid in Alzheimer's Disease

Umur A. Kayabasi¹, Robert C. Sergott²

¹World Eye Hospital, Istanbul, Turkey; ²Wills Eye Hospital, Philadelphia, PA, USA

Introduction: 
Our aim was to detect tau tangles and beta amyloid plaques in retina for the early diagnosis of Alzheimer's Disease (AD).

Methods: 
We examined 30 patients with mild cognitive insufficiency (MCI) and 15 age-matched healthy controls. Retina was examined by fundus autofluorescein (FAF) and optical scanning tomography (OCT) tests. FAF detected lipofuscin which contained beta amyloid in AD and the layer of the accumulations was detected by OCT. Patients who had retinal lesions were given curcumin with proprietary curcumin-phosphatidylcholine phytosome complex for three days and FAF-OCT tests were repeated. All the suspicious cases for AD were sent for brain PET-CT imaging.

Results: 
In 22 patients, tau tangles and plaques were observed on OCT. Curcumin stained the retinal lesions in all 22 patients. Since curcumin binded to beta amyloid, it was proven that the plaques were related to AD. All 22 patients had brain PET-CT results consistent with bilateral temporo-parietal hypometabolism. Tau tangles and curcumin staining was not seen in the control group.

Conclusions: 
Our study suggests that tau tangles and beta amyloid plaques can be seen in retina in an easier way and probably earlier than the brain changes in AD. This is the first study that reveals tau tangles and beta amyloid imagings in alive AD patients with FDA approved devices.

References: None.

Keywords: Tau Tangles, Beta Amyloid, OCT, FAF, Alzheimer's Disease

Financial Disclosures: The authors had no disclosures.

Grant Support: None.
Role of the Optic Canal Size on the Severity of Papilledema and Visual Outcome in Idiopathic Intracranial Hypertension (IIH)

Samuel Bidot¹, Lindsay Clough¹, Amit M Saindane², Nancy J Newman¹,³,⁴, Valerie Biousse¹,³, Beau B Bruce¹,³,⁵

¹Department of Ophthalmology, Emory University School of Medicine, Atlanta, GA, USA, ²Department of Radiology and Imaging Science, Emory University School of Medicine, Atlanta, GA, USA, ³Department of Neurology, Emory University School of Medicine, Atlanta, GA, USA, ⁴Department of Neurological Surgery, Emory University School of Medicine, Atlanta, GA, USA, ⁵Department of Epidemiology, Emory University, Atlanta, GA, USA

Introduction:
High-grade papilledema is a risk factor for visual loss in IIH, but factors contributing to the severity of papilledema remain unclear. We recently found an association between larger bony optic canal size and worse papilledema among IIH patients with highly asymmetric papilledema.¹ Our goal was to confirm these results in a large sample of IIH patients.

Methods:
Retrospective review of definite IIH patients with 1-mm isotropic volumetric pre- or post-contrast T1-weighted brain MRI allowing for optic canal measurement seen between 2009 and 2014. Clinical characteristics/HVF results were reviewed; papilledema was graded according to the modified Frisen scale² on fundus photographs. Cross-sectional area of the optic canals was measured independently 3 times by two readers and averaged for each canal. For each patient, we included the optic canal measurement on the eye with worst papilledema or on the right eye in case of symmetric papilledema. Logistic regression modeling was applied.

Results:
69 IIH patients were included [mean age: 33; 91% women; 65% black; 94% with BMI≥25]. The inter-grader agreement for optic canal measurement was strong (intraclass correlation: 0.77 [95%CI: 0.69-0.83]). Mean±SD optic canal size was 22.9±5mm². Controlling for age, gender, BMI, race, and CSF opening pressure, each mm² increase in canal size was associated with a 0.37 dB reduction in automated perimetry mean deviation (p=0.04); this was likely mediated by the increased odds of grade 4-5 papilledema or optic atrophy in patients with larger canals (OR: 1.24 [95%CI: 1.06-1.46; p=0.007] for grade 4-5 papilledema or atrophy vs. grade <4 papilledema per mm² increase in canal size).³

Conclusions:
Poorer visual field outcomes and severe papilledema or secondary optic atrophy were associated with a larger optic canal. This suggests that larger optic canal size may be a factor facilitating transmission of CSF pressure to the optic disc, leading to more severe papilledema with resultant worse visual loss.

References:

Keywords: Idiopathic Intracranial Hypertension, Neuroimaging, Optic Canal, Papilledema

Financial Disclosures: The authors had no disclosures.

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A New Pupil Light Reflex Test for Detecting Optic Neuropathy Independent of the Fellow Eye Which Highly Correlates to Visual Field Volume

Randy H Kardon1,2, Susan Anderson1,2, Jade Grimm1, Matt Thurtell1,2, Michael Wall1,2, Pieter Poolman1,2

1University of Iowa College of Medicine/Ophthalmology and Visual Sciences, Iowa City, IA, USA, 2Iowa City VA Medical Center and the Center of Excellence for the Prevention and Treatment of Visual Loss, Iowa City, IA, USA

Introduction:
Our purpose was to develop and test a new paradigm for detecting optic nerve disease in one eye, independent of the fellow eye, so that patients with bilateral involvement can be diagnosed and monitored using objective pupil responses. We also sought to determine which stimulus light condition and pupil response parameter (transient vs. sustained contraction) would provide the greatest difference between normal and abnormal eyes and the highest correlation with visual field sensitivity.

Methods:
39 patients seen in the neuro-ophthalmology clinic and 44 normal subjects were prospectively tested by computerized pupillometry (NeurOptics DP2000, Irvine, CA) using a 1 second red or blue light stimulus at 1 lux and 400 lux. The percent pupil contraction from baseline pre-stimulus size was calculated for the transient, initial response to the light stimulus and the sustained pupil contraction at 6 seconds following offset of light. Visual fields were obtained using standard kinetic Goldmann perimetry and the volume of visual field sensitivity was determined and correlated with pupil responses.

Results:
We found the greatest statistically significant separation between eyes of normal subjects vs. those with optic neuropathy occurred with the transient pupil contraction using the 1 second, 400 lux blue light, compared to the sustained post-illumination contraction. In response to 400 lux blue light, the transient contraction gave the highest correlation with volume visual field (r=0.85) compared to the sustained contraction (r=0.52).

Conclusions:
The transient pupil contraction to bright blue light provides an objective, easily recordable reflex, which correlates well with visual field sensitivity. Under these stimulus conditions, both photoreceptor input and direct activation of photosensitive retinal ganglion cells summate the visual field input to the brain. This approach provides a clinical tool for estimating visual dysfunction that has important applications for remote diagnosis and monitoring of vision threatening disorders.

References: None.

Keywords: Pupils, Optic Neuropathy, Visual Field

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Monday, February 23, 6:45 - 7:00 p.m.

Color Vision Deficits in Multiple Sclerosis

Neda Ansari\textsuperscript{1}, Reza Vosoughi\textsuperscript{1}, Kathleen T Mullen \textsuperscript{2}, Ambereesh Pandey\textsuperscript{1}, Behzad Mansouri\textsuperscript{1,3,4}

\textsuperscript{1}Section of Neurology, Department of Internal Medicine, University of Manitoba, Winnipeg, MB, Canada, \textsuperscript{2}MGill Vision Research Unit, Ophthalmology Department, McGill University, Montreal, QC, Canada, \textsuperscript{3}Ophthalmology Department, University of Manitoba, Winnipeg, MB, Canada, \textsuperscript{4}Biomedical Engineering Program, Department of Computer and Electrical Engineering, University of Manitoba, Winnipeg, MB, Canada

Introduction:
Color vision deficits have been reported in multiple sclerosis (MS) in the absence of optic neuritis (ON). Demyelination of the optic nerve in ON probably causes color-vision deficits by affecting the parvocellular-Red/Green (PC/RG) and koniocellular-Blue/Yellow (KC/BY) pathways. The evidence for selective deficits in PC/RG versus KC/BY pathways, however, is inconclusive. Moreover, the mechanism of color vision deficit in MS without ON demyelination is unclear. In this study we investigate color vision deficits in early versus late MS in the PC/RG versus KC/BY pathways.

Methods:
Participants were either early-MS (<1 year after diagnosis, 16 subjects) or late-MS (5-10 years after diagnosis, 15 subjects) with no history of ON. Twenty controls completed the study. Contrast detection thresholds were measured for Achromatic, RG and BY sinewave gratings with spatial frequencies (SF) of 0.5 and 2 cycles-per-degree (cpd) using an orientation discrimination two-alternative forced-choice staircase task.

Results:
We found a significant difference (p<0.05) in RG contrast thresholds at the low SF (0.5 cpd) in early- versus late-MS (mean=2.7 +/- 0.15 and 3.9 +/- 0.16, respectively). Early-MS subjects were similar to the controls. At 2 cpd, mean BY contrast thresholds in early- and late-MS groups were significantly higher than in the controls (BY threshold=5.85% (controls), 9.79 % (early-MS), and 9.04% (late-MS)).

Conclusions:
Here we report for the first time that color contrast sensitivity for RG versus BY color vision is differentially affected in early- versus late-MS. The BY axis is affected in both conditions but the RG axis is affected only in late-MS. These findings are important because 1. BY versus RG color tests may be used in differentiating MS chronicity, 2. Help understand the mechanism of color sensitive pathway involvement in MS in the absence of demyelination, and 3. Show that standard Ishihara color tests are not sufficient in testing MS patients as they exclude the BY axis.

References:

Keywords: Multiple Sclerosis, Color Vision, Parvocellular, Koniocellular

Financial Disclosures: The authors had no disclosures.

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