5:00 p.m. - 5:15 p.m.  
**Steven F. Stasheff, MD, PhD**  
Improved ganglion cell light responsiveness following induced pluripotent stem cell (iPSC) transplantation in a model of Leber’s congenital amaurosis (LCA)

5:15 p.m. - 5:30 p.m.  
**Patric Sibony, MD**  
Geometric Morphometrics of the Peripapillary SD-OCT: shape analysis of the RPE layer in papilledema and ischemic optic neuropathy

5:30 p.m. - 5:45 p.m.  
**Jeffrey Bennett, MD, PhD**  
Aquaporumab: An Anti-Aquaporin-4 Monoclonal Antibody Blocker Therapy for Neuromyelitis Optica

5:45 p.m. - 6:00 p.m.  
**Madhura Tamhankar, MD**  
Microvascular vs. Non-Microvascular Third, Fourth, and Sixth Nerve Palsies: A Prospective Multi-Center Study to Determine Etiology.

6:00 p.m. - 6:15 p.m.  
**Randy Kardon, MD, PhD**  
Automated Quantification of Volumetric Optic Disc Swelling in Papilledema Using Spectral-Domain Optical Coherence Tomography (OCT)

6:15 p.m. - 6:30 p.m.  
**Stephen Moster**  
Five- to Seven-Year Longitudinal Data for Vision and OCT Retinal Nerve Fiber Layer (RNFL) Thickness in MS

6:30 p.m. - 6:45 p.m.  
**Mithu Storoni**  
The Use Of Magnetic Resonance Imaging To Distinguish Between NMO Spectrum And MS Related Optic Neuritis Based On The Appearance Of The Visual Pathways

6:45 p.m. - 7:00 p.m.  
**Andrew Lee, MD**  
Optic Disc Edema, Globe Flattening, Choroidal Folds, and Hyperopic Shifts Observed in Astronauts after Long-duration Space Flight
Monday, February 13, 2012, 5:00 p.m. - 5:15 p.m.

Improved ganglion cell light responsiveness following induced pluripotent stem cell (iPSC) transplantation in a model of Leber's congenital amaurosis (LCA)

Steven F Stasheff, Michael P Andrews, Budd Tucker, Malini Shankar

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Introduction:
We describe characteristic deterioration in spontaneous and light-evoked electrophysiologic activity of retinal ganglion cells in an animal model of Leber's congenital amaurosis (LCA), the most common genetic cause of early childhood blindness. To date LCA remains incurable, although transplantation of induced pluripotent stem cells (iPSCs) has been shown to restore visual function in other severe retinal degenerations. We also report here the preliminary finding that subretinal iPSC transplantation can forestall the deterioration of light-evoked responses in mice with the most common LCA mutation.

Methods:
Multielectrode recordings of ganglion cells were made in the in vitro retina of mice with the most common mutation in the ciliary protein gene Cep290. Multiple spatiotemporal parameters were compared quantitatively with those in wild-type (wt) retinas to assess dynamic properties of developmental waves; time course of emerging hyperactivity and diminishing light responses; and amplitude, threshold, transiency and duration of light-evoked responses. These same measures of ganglion cell activity were made in a Cep290/- retina treated by subretinal injection of iPSCs derived from fibroblasts of wt dsRed mice.

Results:
Early developmental waves of spontaneous bursting were normal in Cep290/- ganglion cells. Sustained spontaneous hyperactivity developed almost immediately following first eye opening, and light-evoked responses were diminished from this age and deteriorated very gradually after that. Compared with the retina of an untreated Cep290/- mouse, about twice as many ganglion cells exhibited robust light-evoked responses in a retina that underwent transplantation of wt iPSCs at postnatal day 14 (P14).

Conclusion:
Progressive changes in spontaneous and light-driven ganglion cell activity characterize the Cep290/- mouse model of LCA, with spatiotemporal features distinct from those of other retinal degenerations. Preliminary findings indicate the potential of iPSC transplantation to preserve or restore visual function in LCA, and encourage further optimization of the time window for transplantation to maximal treatment effectiveness.

References: None

Key Words: retinal degeneration, Leber's congenital amaurosis, stem cell transplantation, electrophysiology, retinal ganglion cell

Financial Disclosure: The authors had no disclosures.
Geometric Morphometrics of the Peripapillary SD-OCT: shape analysis of the RPE layer in papilledema and ischemic optic neuropathy

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Introduction:
Geometric Morphometrics (GM) is an analytic technique used to quantify and statistically assess variation in the shape of biological forms and their covariation with other variables. This methodology defines shape as the geometric property of a form that remains after filtering out variations due to differences in position, scale and orientation. GM was used to analyze the shape of the peripapillary retinal-pigment-epithelium Bruch’s-membrane layer (RPE/BM) imaged on the SD-OCT 5-line raster in patients with papilledema and ischemic optic neuropathy compared to normals.

Methods:
We compared three groups of subjects: 30 normals, 20 with anterior ischemic optic neuropathy (AION) and 25 papilledema with intracranial hypertension. We digitized 20 equidistant semilandmarks on OCT images of the RPE/BM layer spanning 2500 microns on each side of the neural canal opening (NCO). The data was analyzed using standard GM techniques including a Generalized Least Squares Procrustes Superimposition, Principal Component Analysis, thin-plate spline (to visualize deformations); and permutation statistical analysis to evaluate differences in shape variables.

Results:
The RPE/BM layer in normals and AION have a characteristic V-shape pointing away from the vitreous; the RPE/BM layer in papilledema has an inverted-U shape skewed nasally inward toward the vitreous. The differences were statistically significant. There was no significant difference in shapes between normals and AION. Pre and post treatment OCTs, in selected cases of papilledema shows that the inverted-U shaped RPE/BM moved posteriorly into a normal V-shape as the papilledema resolved with weight loss or shunting.

Conclusion:
The shape difference in papilledema, absent in AION, cannot be explained by disc edema alone. The difference is a consequence of both the transliminar pressure gradient and the material properties of the peripapillary sclera. GM offers a novel method of statistically assessing shape differences of the peripapillary optic nerve head.

References:

Key Words: Optical Coherent Tomography, Shape analysis, Papilledema, Ischemic optic neuropathy, Intracranial hypertension

Financial Disclosure: The authors had no disclosures.
Monday, February 13, 2012, 5:30 p.m. – 5:45 p.m.

Aquaporumab: An Anti-Aquaporin-4 Monoclonal Antibody Blocker Therapy for Neuromyelitis Optica

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Introduction:
Neuromyelitis optica (NMO) is an inflammatory demyelinating disease that predominantly affects the optic nerves and spinal cord. Circulating autoantibodies (NMO-IgG) against the astrocyte water channel aquaporin-4 (AQP4) cause complement- and cell-mediated astrocyte damage with consequent neuroinflammation and demyelination. Within five years of diagnosis, more than 50% of individuals are visually impaired or require ambulatory assistance. Current NMO therapies include non-specific prophylactic immunosuppression and plasma exchange for acute exacerbations.

Methods:
We engineered non-pathogenic recombinant monoclonal anti-AQP4 antibodies (‘aquaporumab’) to selectively block NMO-IgG binding to AQP4 in the absence of effector function. Aquaporumab comprises a tight-binding anti-AQP4 Fab and a mutated Fc that lacks functionality for complement- and cell-mediated cytotoxicity. Aquaporumab was tested for its ability to block NMO-IgG-mediated cytotoxicity in vitro, ex vivo, and in vivo using cell culture, spinal cord explant, and animal models.

Results:
Aquaporumab significantly blocked NMO-IgG induced cytotoxicity in vitro. In AQP4-expressing cell cultures, aquaporumab inhibited complement-mediated cytotoxicity by 90% (P < 0.001) and cell-mediated cytotoxicity by 84% (P < 0.001). In an ex vivo spinal cord explant model, aquaporumab markedly reduced NMO-IgG-mediated astrocyte loss and demyelination. Last, in an in vivo mouse model, blocking antibody significantly reduced NMO-IgG mediated AQP4 and myelin loss (P < 0.01).

Conclusion:
The efficacy of aquaporumab blocking antibody supports a primary role of NMO-IgG in disease pathogenesis and introduces the possibility of targeted therapy for acute and prophylactic treatment. Blocker therapy to prevent binding of pathogenic autoantibodies to their targets may be useful for the treatment of other autoimmune diseases.

References:

Key Words: Neuromyelitis optica, aquaporin-4, therapy, monoclonal antibody

Financial Disclosure: Jeffrey Bennett has filed for intellectual property on aquaporumab therapy. Alan Verkman has filed for intellectual property on aquaporumab therapy. The remaining authors had no disclosures.
Microvascular vs. Non-Microvascular Third, Fourth, and Sixth Nerve Palsies: A Prospective Multi-Center Study to Determine Etiology.

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Introduction:
The role for early neuroimaging in patients older than 50 years presenting with isolated 3rd, 4th or 6th nerve palsy remains controversial. While some authors recommend waiting 3-6 months for spontaneous resolution to occur before imaging older patients with isolated 3rd, 4th, or 6th nerve palsies,1,2,3 others recommend that MRI and other studies be performed early.4,5

Methods:
Patients older than 50 years of age with isolated 3rd, 4th and 6th nerve palsy presenting within a month of symptom onset were prospectively evaluated at 10 neuro-ophthalmic tertiary referral centers. All patients underwent gadolinium enhanced MRI. The number of patients with structural lesions on MRI scan responsible for their palsy was noted. All patients were followed for 3-6 months after presentation to determine outcomes.

Results:
Among 96 patients, the average age was 65±12 years; 57 patients were men. There were 17 patients with 3rd, 21 with 4th and 58 with 6th nerve palsy. Overall, 85% (82/96 patients) were diagnosed with vasculopathic palsies, while 14.5% (14/96) had other causes for their palsy. Of the 96 patients, 30 with presumed vasculopathic palsies had prospective MRI of the brain ordered by the examining neuro-ophthalmologist. Of these, 4 patients were found to have intracranial lesions responsible for their palsy, including lymphoma involving the cavernous sinus, petroclival meningioma, infarct of the posterior midbrain and enhancement of the third nerve related to inflammation. In this sub-group of patients with MRI lesions, the diagnostic yield of the MRI scan was 13%.

Conclusion:
In this prospective, multi-center cohort of patients over age 50 years, a substantial proportion with isolated 3rd, 4th and 6th nerve palsy had non-microvascular structural causes for their palsy while some studies have recommended careful follow up without neuro-imaging based on a low diagnostic yield of MRI in patients with presumed vasculopathic palsies4, our results demonstrate that many patients had other etiologies that altered immediate patient management. Our results suggest that early neuroimaging has a role in the evaluation of adults with acute ocular motor mononeuropathies.

References:

Key Words: ocular motor palsy, diplopia, Neuro-imaging

Financial Disclosure: The authors had no disclosures.
Automated Quantification of Volumetric Optic Disc Swelling in Papilledema Using Spectral-Domain Optical Coherence Tomography (OCT)

Randy Kardon1, Jui-Kai Wang2, Mark J Kupersmith4, Mona Garvin3

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Introduction:
Better methods of quantifying papilledema over time with OCT are needed due to algorithm failures at segmenting the retinal nerve fiber layer and total retinal thickness. To solve this problem, we have developed an automated robust image analysis method for the quantification of volumetric optic disc swelling in papilledema subjects using spectral-domain optical coherence tomography (SD-OCT) and have validated it.

Methods:
A custom image-analysis algorithm was developed to derive total retinal/disc volume measurements from SD-OCT scans of subjects with papilledema. The derived volumes were correlated with peripapillary RNFL and peripapillary total retinal thickness measures as well as with Frisén grading.

Results:
In 71 SD-OCT scans, the mean (± standard deviation) resulting total retinal/disc volumes for Frisén scale 0 to scale 4 were 11.36±0.56, 12.47±1.20, 14.41±2.08, 17.48±2.63, and 21.81±3.16 mm³, respectively. The Spearman rank correlation coefficient was 0.743. Using 55 eyes for which valid Zeiss RNFL measurements were available, Pearson’s correlation coefficient (r) between the total retina/disc volume and our software segmentation of the peripapillary TR thickness and RNFL thickness, and the Zeiss’ RNFL thickness was 0.980, 0.929, and 0.946, respectively. Between Zeiss’ RNFL and our RNFL thickness, r was 0.901; with our TR thickness, r was 0.961.

Conclusion:
Volumetric measurements of the degree of disc swelling in subjects with papilledema can be obtained from SD-OCT volumes, with the mean volume appearing to be linearly related to the Frisén scale grade. The volume measurement overcomes the problem of failures in the software algorithms for RNFL associated with papilledema. Using such an approach can provide a more continuous and objective means for assessing the degree of disc swelling and monitoring changes with treatment over time.

References:

Key Words: Papilledema, Optical Coherence Tomography, Optic Nerve Imaging, Idiopathic Intracranial Hypertension

Financial Disclosure: Randy Kardon - consultant for Novartis for steering committee for OCTiMS Multicenter Study. The remaining authors had no disclosures.
Five- to Seven-Year Longitudinal Data for Vision and OCT Retinal Nerve Fiber Layer (RNFL) Thickness in MS

Stephen Moster, Lauren Talman, James Wilson, Kristin Galetta, Reiko Sakai, Steven Galetta, Elliot Frohman, Peter Calabresi, Laura Balcer

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Introduction:
Retinal nerve fiber layer (RNFL) thinning by optical coherence tomography (OCT), a marker for MS visual pathway axonal loss, has been evident in short longitudinal studies lasting less than 3 years. Patterns of thinning over longer time periods have not been established. We examined peripapillary RNFL thinning at 3 years and beyond in a multi-center collaborative MS cohort.

Methods:
Patients with MS underwent time-domain OCT measurement of peripapillary RNFL thickness as part of a longitudinal study starting in 2005. OCT, low-contrast acuity (2.5%, 1.25%), and visual acuity (VA) were assessed at baseline and at 6-12-month intervals. Eyes that developed acute ON during follow-up were not included in these analyses; history of ON prior to enrolment was captured.

Results:
MS eyes with long-term follow-up in this cohort (n=381, 196 patients) demonstrated RNFL thinning from baseline that was significant starting at the 2-3-year interval (P=0.001) and continued through the 6-7-year follow-up period (P=0.006 vs. the 6-12-month interval, GEE models accounting for age and within-patient, inter-eye correlations). These patterns were observed for eyes with or without prior history of ON; average RNFL thinning was 1.9 microns per year of follow-up in both groups (P<0.001). Eyes with clinically significant visual loss showed greater RNFL thinning over time compared to eyes with stable vision (P<0.001 for low-contrast and VA, logistic regression). Proportions of eyes with RNFL loss greater than test-retest variability (≥6.6 microns) increased from 19% at 1-2 years to 56% at 5-6 years (P<0.001, chi-square test for trend).

Conclusion:
Progressive RNFL thinning occurs during long-term follow-up of patients with MS. This is observed even in the absence of ON, and is associated with clinically significant visual loss. Sub-clinical axonal loss in the anterior visual pathway is likely to be an important contributor to visual dysfunction, and should be the target of new clinical trials for neuroprotection.

References:

Key Words: multiple sclerosis, optical coherence tomography (OCT), low-contrast acuity, neuroprotection

Financial Disclosure: Dr. Galetta has received honoraria from Biogen-Idec, Teva, and Novartis. Dr. Calabresi has received personal compensation for consulting and serving on scientific advisory boards from Biogen Idec, Teva, Vaccinex, Abbott, and Novartis; Dr. Calabresi has also received research funding from Biogen Idec, Teva, EMD Serono, Vertex, Genentech, Abbott, and Bayer. Dr. Frohman has received speaker fees from Biogen, Teva, Novartis, Acorda and Bayer. He has received consulting fees from Biogen, Teva, Acorda, Novartis and Abbott. Dr. Balcer has received honoraria from Biogen-Idec, Novartis, Bayer and Vaccinex. The remaining authors had no disclosures.
Monday, February 13, 2012, 6:30 p.m. – 6:45 p.m.

The Use Of Magnetic Resonance Imaging To Distinguish Between NMO Spectrum And MS Related Optic Neuritis Based On The Appearance Of the Visual Pathways

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Introduction:
Since the discovery of the anti-Aquaporin 4 antibody, no comparison has been made of the appearance of the visual pathway during an episode of acute optic neuritis in the context of MS and NMO spectrum disease. This study investigates whether the MR image of the visual pathways in acute optic neuritis offers clues as to its underlying aetiology

Methods:
The MR scans of 11 NMO spectrum patients and 16 MS patients with optic neuritis were retrospectively analysed independently by two Neuroradiologists. The presence of an increased 'cross-sectional area' was used as an absolute marker for the site of inflammation secondary to the current episode of acute optic neuritis. The sites affected within the visual pathway were noted and each patient was given a score to account for their 'lesion extent' during the episode of acute optic neuritis. A 2-dimensional perspective was assumed in the scoring.

Results:
Patients with MS demonstrated a mean score of 2.3 (range 1-6) whereas patients with NMO spectrum demonstrated a mean score of 4.2 (range 2-7) of lesion extent. This was statistically significant (P=0.003). A score of greater than 6 was only seen in patients with NMO spectrum disorder. When using a cutoff score of greater or equal to 4, the sensitivity was 55% and the specificity was 94%. When examined in aggregate, the relative risk for an NMO spectrum patient having intracranial, chiasmal and tract involvement during an episode of optic neuritis compared to an MS patient was 7.27 (95% confidence interval between 0.98 and 54.0; p=0.15).

Conclusion:
The MR image of the visual pathways alone may allow NMO related optic neuritis to be identified from MS related optic neuritis on the basis of a ‘lesion extent score’ and sites affected.

References: None

Key Words: optic neuritis, NMO, MS, Neuroimaging

Financial Disclosure: The authors had no disclosures.
Disc Edema, Globe Flattening, Choroidal Folds, and Hyperopic Shifts Observed in Astronauts after Long-duration Space Flight.

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Introduction:
The purpose of this study was to describe the history, clinical findings, and possible etiologies of ophthalmic findings discovered in 7 astronauts after long-duration space flight, and document vision changes in approximately 300 additional astronauts.

Methods:
Retrospective, observational examination of ophthalmic findings in 7 astronauts and analysis of post-flight questionnaires regarding in-flight vision changes in approximately 300 additional astronauts.

Seven astronauts with ophthalmic anomalies upon return from long-duration space missions to the International Space Station and 300 additional astronauts who completed post-flight questionnaires regarding in-flight vision changes.

Before and after long-duration space flight, all 7 subjects underwent complete eye examinations, including cycloplegic and/or manifest refraction and fundus photography. Six underwent post-mission optical coherence tomography (OCT) and magnetic resonance imaging (MRI); 4 had lumbar punctures (LP). Approximately 300 astronauts were queried regarding visual changes during space missions.

Results:
After 6 months of space flight, 7 astronauts had ophthalmic findings, consisting of disc edema in 5, globe flattening in 5, choroidal folds in 5, cotton wool spots (CWS) in 3, nerve fiber layer thickening by OCT in 6, and decreased near vision in 6 astronauts. Five of 7 with near vision complaints had a hyperopic shift ≥+0.50 diopters (D) between pre/post-mission spherical equivalent refraction in 1 or both eyes (range, +0.50 to +1.75 D). These 5 showed globe flattening on MRI. Lumbar punctures performed in the 4 with disc edema documented opening pressures of 22, 21, 28, and 28.5 cm H(2)O performed 60, 19, 12, and 57 days post-mission, respectively. The 300 post-flight questionnaires documented that approximately 29% and 60% of astronauts on short and long-duration missions, respectively, experienced a degradation in distant and near visual acuity. Some of these vision changes remain unresolved years after flight.

Conclusion:
We hypothesize that the optic nerve and ocular changes we describe may result from cephalad fluid shifts brought about by prolonged microgravity exposure. The findings we report may represent parts of a spectrum of ocular and cerebral responses to extended microgravity exposure.

References: None

Key Words: optic disc edema, choroidal folds, astronauts, papilledema

Financial Disclosure: The authors had no disclosures.