PLATFORAM SESSION II
Tuesday, February 14, 2012 • 7:30 a.m. – 12:00 p.m.

Moderators: Alfredo A. Sadun, MD, PhD and Michael S. Lee, MD – before break
Moderators: Nicholas J. Volpe, MD and Janine L. Johnston, MD, FRCP(C) – after break

7:30 a.m. - 7:45 a.m.  Bryan D. Riggeal, MD
Does the Presence of Transverse Sinus Stenosis (TSS) Influence the Clinical Presentation and Outcome of Idiopathic Intracranial Hypertension (IIH)?

7:45 a.m. - 8:00 a.m.  Ruth Huna-Baron, MD
Reduced Macular Thickness and Color Vision in Parkinson’s Disease

8:00 a.m. - 8:15 a.m.  Patrick Yu-Wai-Man, BMEdSci, MBBS, PhD, MRCOphth
Mitofusin 2 (MFN2) mutations cause mitochondrial DNA instability in Charcot-Marie-Tooth disease

8:15 a.m. - 8:30 a.m.  Christian Lueck, PhD, FRACP
Comparison of Multifocal Objective Pupil Perimetry and MRI in Multiple Sclerosis

8:30 a.m. - 8:45 a.m.  Sashank Prasad, MD
Occipital Areas Distinguish Semantic Content in Congenitally Blind but not Sighted Individuals

8:45 a.m. - 9:00 a.m.  Karen Schmitt, MD
Transmeningeal Drug Delivery to the Optic Nerve

9:00 a.m. - 9:15 a.m.  Kimberly Winges, MD
Macular Thickening by OCT In a Phase III Trial of Fingolimod: The Importance of Quality Control

9:15 a.m. - 9:30 a.m.  Update: The Journal of Neuro-Ophthalmology
Lanning Kline, MD, Editor-in-Chief and Jason Roberts, PhD, Managing Editor

9:30 a.m. - 10:00 a.m.  Coffee Break: Grand Oaks A - F

10:00 a.m. - 10:15 a.m.  Mário Monteiro, MD
Macular Thickness Measurements with Optical Coherence Tomography for Quantification of Axonal loss in Chronic Papilledema from Pseudotumor Cerebri Syndrome

10:15 a.m. - 10:30 a.m.  Gerry Maitland, MD
Contrast Sensitivity Visual Acuity Is Deficient In Parkinson’s Disease And Degrades Multiple Aspects Of Motor Performance Under Conditions Of Dim Illumination
(Platform Session II Continued)

10:30 a.m. - 10:45 a.m.  Sean Kennedy, MD  
Effects of Induced Monocular Blur versus Anisometropic Amblyopia on Saccadic Eye Movements

10:45 a.m. - 11:00 a.m.  Michael Wall, MD  
Idiopathic Intracranial Hypertension Treatment Trial (IIHTT) Update

11:00 a.m. - 11:15 a.m.  Konrad P. Weber, MD  
Single motor unit recordings of ocular vestibular evoked myogenic potentials in human extraocular muscles

11:15 a.m. - 11:30 a.m.  Ivana DeDomenico, PhD  
A murine model of giant cell arteritis: Infection with a Burkholderia pseudomallei-like strain treated with steroids and antibiotics

11:30 a.m. - 11:45 a.m.  Bonnie Keung, MD  
Treatment of Subjects with Giant Cell Arteritis with Antibiotics

11:45 a.m. - 12:00 p.m.  Mark Kupersmith, MD  
Distinguishing Retinal Nerve Fiber Layer Injury by Optical Imaging in Acute Optic Nerve Head Swelling
Tuesday, February 14, 2012, 7:30 a.m. – 7:45 a.m.

Does the Presence of Transverse Sinus Stenosis (TSS) Influence the Clinical Presentation and Outcome of Idiopathic Intracranial Hypertension (IIH)?


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Introduction:
TSS is common in IIH, but its effect on the course and outcome of IIH is unknown. We evaluated differences in characteristics and visual outcomes between IIH patients with and without TSS.

Methods:
All IIH patients seen in our institution between 9/2009 and 9/2011 who underwent brain MRV or CTV were included. Patients were separated into two groups based on the presence or absence of TSS. Patient characteristics, presenting symptoms/signs, and visual outcomes were recorded. All visual fields (VF; HVF/GVF) were graded as [1]=normal; [2]=blind spot enlargement; [3]=nasal/temporal defect; or [4]=diffuse constriction. Univariate statistics and linear regression were applied.

Results:
134 patients were included: 49 with TSS (48 bilateral), 85 without TSS. There were no differences between the two groups with respect to mean age (29 vs. 27 years, p=0.26), black race (53% vs. 42%, p=0.23), female sex (92% vs. 84%, p=0.17), mean BMI (36 vs. 37, p=0.38), or mean CSF-OP (38 cm vs. 38 cm, p=0.99). Headache frequency in the two groups was similar at baseline (82% vs. 81%, p=0.95) and at last follow up (41% vs. 50%, p=0.36). Grade of papilledema, visual acuity, and VF were similar at baseline, but initial HVF mean deviation (HVF-MD) was better in the TSS group than in the no-TSS group (-4.8 vs. -6.8, p=0.08). There was no medical or surgical therapy difference by TSS status. At last follow-up, grade of papilledema, visual acuity, and VF were similar. However, the no-TSS group had significantly more improvement in VF-grade (-0.60 vs -0.28, p=0.049) and HVF-MD (3.0 vs. 1, p=0.026) than the TSS group. Linear regression suggested that the worse HVF-MD among no-TSS patients at baseline better predicted their degree of improvement than the patient’s TSS status.

Conclusion:
While TSS was found in 37% of IIH patients, the presence of TSS did not have a substantial impact on outcomes. Our findings do not support routine TSS stenting in IIH.

References:

Key Words: idiopathic intracranial hypertension, transverse sinus stenosis, visual outcomes

Financial Disclosure: The authors had no disclosures.
Reduced Macular Thickness and Color Vision in Parkinson's Disease

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Introduction:
Parkinson's disease (PD) is the second most common neurodegenerative disorder in the developed world. Visual disturbances are prominent among the non-motor aspects of PD. We investigated the correlation between retinal morphology and both (1) visual functions, and (2) disease severity in PD patients.

Methods:
We conducted a prospective age-matched study. Participants underwent comprehensive neurological and ophthalmological examinations. A high resolution spectral domain optical coherence tomography (HD-OCT) was used to determine peripapillary retinal nerve fiber layer (RNFL), macular thickness and volume.

Results:
Forty eight PD and 16 control eyes participated. Macular average thickness was significantly reduced in PD (275.4 ±17.4 vs. 286.9±10.3 μm, p=0.0026), as well as macular volume (9.93±0.82 vs. 10.34±0.36 mm³, p=0.007). Mean age was 62.3±8.0 vs. 58.1±9.3 years p=0.284). Inferior quadrant RNFL was thinner in PD 119.9±18.7 vs. controls 128.4±13.1 μm, p=0.049.

The color vision was reduced in PD patients (4.61±1.22 vs. 5.13±0.34 p=0.009). Correlation analysis of OCT variables (RNFL, macular thickness and volume) and visual variables (color vision and contrast) revealed significant relation between macular volume and color vision (r=0.549, p= 0.00023) in PD patients. Mean RNFL and macular thickness did not significantly correlat with motor Unified Parkinson's disease rating scale.

Conclusion:
The results show that macular thickness is reduced in PD patients. This finding is more prominent than the RNFL thinning. OCT parameters correlated with significant reduction in color vision observed in our PD patients. This correlation had not been described before. Macular thickness and RNFL reduction have been reported in smaller groups of PD patients using earlier time- domain OCT. Our results, using spectral domain HD-OCT with superior resolution and stability, confirm these findings in a larger age-matched group and also establish the correlation with decreased color vision.

References:

Key Words: OCT, Parkinson's disease, color vision

Financial Disclosure: The authors had no disclosures.
Tuesday, February 14, 2012, 8:00 a.m. – 8:15 a.m.

Mitofusin 2 (MFN2) mutations cause mitochondrial DNA instability in Charcot-Marie-Tooth disease

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Introduction:
Charcot-Marie-Tooth (CMT) disease is a heterogeneous group of inherited peripheral neuropathies and it affects at least 1 in 2,500 individuals.¹,² A specific autosomal-dominant axonal CMT subtype, hereditary motor and sensory neuropathy type VI (HMSN-VI, OMIM 601152), is caused by mutations in mitofusin 2 (MFN2, 1p36.2).³ In addition to early-onset severe peripheral neuropathy, affected individuals also develop progressive optic nerve dysfunction in later childhood. MFN2 is a critical mitochondrial outer membrane protein and it shares a remarkable degree of structural and functional complementarity with OPA1, a mitochondrial inner membrane protein implicated in the majority of cases of autosomal-dominant optic atrophy (ADOA, OMIM 165500).⁴,⁵ The aim of this study was to provide new mechanistic insights by investigating the deleterious influence of MFN2 mutations on mitochondrial biogenesis.

Methods:
Tissue samples were available from 48 patients with confirmed MFN2 mutations. Using well-established molecular protocols, various markers of mitochondrial dysfunction were assayed including: (i) mitochondrial DNA (mtDNA) proliferation in blood leukocytes, (ii) the presence of biochemically-defective cytochrome c oxidase (COX) fibres in skeletal muscle biopsies, and (iii) the kinetics of mtDNA repopulation in fibroblast cultures after ethidium bromide-induced depletion.

Results:
Blood leukocytes from MFN2-positive patients had significantly increased mtDNA copy numbers (Mean = 205.9, n = 48) compared with age-matched controls (Mean = 60.9, n = 131; p < 0.0001). Significant mtDNA proliferation was also evident in skeletal muscle fibres from MFN2-positive patients. COX-negative skeletal muscle fibres were present and these harboured high levels of somatic mtDNA deletions, accounting for the observed respiratory chain defect. MFN2-positive fibroblasts had significantly impaired rates of mtDNA repopulation following a period of increased cellular stress.

Conclusion:
The MFN2 protein is intricately involved in mtDNA maintenance and the faithful replication of the mitochondrial genome. Pathogenic MFN2 mutations ultimately lead to neuronal cell loss by triggering a mitochondrial biochemical defect.

References:

Key Words: Charcot-Marie-Tooth disease, Mitofusin 2 mutations, Mitochondrial disease, Neurodegeneration

Financial Disclosure: The authors had no disclosures.
Comparison of Multifocal Objective Pupil Perimetry and MRI in Multiple Sclerosis

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Introduction:
Magnetic resonance imaging (MRI) is widely used as a surrogate marker in the assessment of patients with multiple sclerosis (MS). An alternative to MRI which was equally informative but cheaper, more patient-friendly, and more easily accessible would be highly desirable. Multifocal objective pupil perimetry (mfPOP) may be suitable.

Methods:
85 subjects with MS (49.8 ± 11.3 yr, 62 women) and 35 normal controls (47.9 ± 16.8 yr, 22 women) were enrolled. 72 patients had relapsing remitting MS (RR), 13 had progressive MS (PS). The mean (± SD) EDSS score was 3.5 ± 1.0 (RR) and 5.9 ± 1.4 (PS). All subjects underwent MRI and mfPOP. MRI measures included T1 and T2 lesion volumes (LVs), brain parenchymal fractions (BPFs), and regional brain volumes (BVs). mfPOP responses were obtained from 44 regions per visual field. Each region was analysed according to response time-to-peak and standardized amplitude (AmpStd). The accuracy of predicting MS disease status was determined from the percentage area under the receiver operator curve (%AUC).

Results:
mfPOP responses showed a significant reduction of 0.69 ± 0.04 dB in AmpStd and a delay in time-to-peak of 25.95 ± 0.89 ms in MS patients; the delay had a trend towards linearity with the EDSS score. There was no significant difference in BPF between MS subjects and controls and, of the BVs, only the basal-ganglia-plus-thalamic volumes in the PS group showed a significant decrease (-1.07 ± 0.4 dB, P = 0.01). mfPOP %AUCs for RR and PS groups were 75.0 ± 3.3 and 94.8 ± 3.6, respectively. For BPF, %AUCs were 61.6 ± 4.9 (RR) and 72.2 ± 6.3 (PS). For BVs they were 63.0 ± 4.4 (RR) and 75.4 ± 7.4 (PS).

Conclusion:
mfPOP is inexpensive and well-tolerated. It has the potential to complement MRI as a surrogate marker for MS disease activity.

References: None

Key Words: multiple sclerosis, pupillometry, MRI, investigation

Financial Disclosure: Andrew James and Teddy Maddess have patents licenced to Seeing Machines Ltd but have no shares or options. They have received research support but not travel from them this year. Teddy Maddess has earned royalty income from Carl Zeiss Meditec for the FDT/Matrix Perimeters. He is on the Scientific Advisory Board of EyeCo Pty Ltd but did not receive payment from them. The remaining authors had no disclosures.
Occipital Areas Distinguish Semantic Content in Congenitally Blind but not Sighted Individuals

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Introduction:
Early visual loss alters structural and functional networks in the brain, but specific effects upon neural representations of distinct semantic information are not well characterized (Connolly 2007; Mahon 2009; Noppeney 2003).

Methods:
We studied fMRI activation patterns during comprehension of spoken language in a population of 10 early-blind participants and 10 sighted controls. We systematically varied the semantic content of the stimuli to represent either visual, tactile, or auditory information (with white noise and reverse language control conditions).

Results:
Bulk activity within striate cortex during language processing was greater for blind than sighted subjects. However, across conditions of varied semantic content in the blind, bulk striate cortex activity was equivalent. On the other hand, multivoxel pattern analysis (Kriegeskorte 2006) demonstrated that striate cortex in the blind (but not the sighted) exhibits above-chance classification accuracy for pair-wise comparisons between semantic categories. Furthermore, whole-brain analysis of classification accuracy (for blind and sighted groups, collapsing across all pair-wise comparisons of semantic categories) revealed that blind subjects possess extensive occipital areas (with left hemispheric predominance) capable of semantic category discrimination.

Conclusion:
While it is well established that occipital areas demonstrate cross-modal plasticity in the setting of early visual loss, these data specify a role of category discrimination within larger semantic processing networks.

References:

Key Words: Blindness, Neuronal Plasticity, Semantic Processing

Financial Disclosure: The authors had no disclosures.
Introduction:
Optic neuropathies are the leading cause of irreversible blindness worldwide and lack adequate treatment options. In order to investigate a novel approach to treatment, we tested the capacity of neuroprotective drugs to cross the optic nerve sheath in vitro.

Methods:
Optic nerves from two pigs at time of death and optic nerves from two humans at time of globe enucleation were harvested. A diffusion cell was designed with optic nerve sheath as membrane to test meningeal penetration by both brimonidine alone and brimonidine encapsulated in nanoparticle (NP-brimonidine). A UV-VIS spectrophotometer was used to measure concentration in the donor and receptor chambers over time.

Results:
Increasing concentration in the receiver chamber was measured in the brimonidine alone and the NP-brimonidine experiments when tested with either pig or human meninges. The human data was fitted with a two parameter exponential regression analysis (brimonidine alone donor \( r^2 = 0.87 \), receiver \( r^2 = 0.795 \); NP-brimonidine donor \( r^2 = 0.79 \), receiver \( r^2 = 0.986 \). The time constant (\( \tau \)) was 10.2 hours (donor) and 13.09 hours (receiver) in the brimonidine study, and 24 hours (donor) and 15.84 hours (receiver) in the NP-brimonidine study. The encapsulated brimonidine had a longer time to reach equilibrium (Figure 1).

Conclusion:
Passage of brimonidine through the optic nerve sheath was demonstrated. The increase in time constants when comparing the NP-brimonidine to the brimonidine curves in the human studies supports that diffusion is delayed by drug being loaded in NP. We envision employing the transmeningeal route using the image-guided orbital endoscope and the novel polyester nanoparticle (NP) drug delivery system created by members of our team for the ultimate goal of sustained-released neuroprotective agents directly delivered to the ganglion cell axons of the optic nerve.

References:
4. Krupin, Liebmann, Greenfield, Ritch, Gardiner, A randomized trial of brimonidine versus timolol in preserving visual function: Results from the low-pressure glaucoma treatment study, American Journal of Ophthalmology, 151, 671-681, 2011

Key Words: Neuroprotection, Nanoparticle, Optic neuropathy, brimonidine

Financial Disclosure: The authors had no disclosures.
Tuesday, February 14, 2012, 9:00 a.m. – 9:15 a.m.

Macular Thickening by OCT In a Phase III Trial of Fingolimod: The Importance of Quality Control

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Introduction:
Cystoid macular edema was documented in a small number of MS patients taking fingolimod (Gilenya, Novartis) in sentinel clinical trials.\(^2\),\(^3\),\(^4\) FDA concern about vision risk has led to a recent statement by the AAO and NANOS, which recommends ophthalmoscopic screening at initiation and followup.\(^1\) The American fingolimod versus placebo phase III trial (FREEDOMS 2) screened patients with time-domain optical coherence tomography (Stratus OCT, Zeiss Microscope) at baseline and over 2 years. We report here the prevalence of macular edema in that population.

Methods:
Data for our observational, retrospective study was obtained from all OCT scans performed in the FREEDOMS 2 study cohort, with enrollment based on clinical criteria published previously.\(^3\) Macular OCT was collected at baseline and at months 1, 3, 6, 18, and 24 (and a few at 4 years). Based on expert consensus, edema was defined as an increase of greater than 20\% over baseline macular thickness for each patient by central foveal thickness (CFT, one A scan) and area (CFA, multiple A-scans within the central 1 mm).

Results:
20,063 scans from 935 patients were collected. 499 (2.5\%) scans in 200 patients demonstrated CFT of 20\% above baseline thickness, with 60 patients thick on both CFA and CFT. On careful review, 449 of these 499 scans were misaligned. 18 scans from 11 patients met criteria but did not show cystoid changes on scan review. 24 scans from 4 patients, however, did show cystoid macular changes by CFT and CFA. Thus, 4 of 935 patients (0.4\%) demonstrated OCT evidence of true macular edema.

Conclusion:
While randomization group assignment is not yet identified, limiting current conclusions of drug association, our results suggest that quality control is imperative in clinical trials using OCT data. Nevertheless, the 0.4\% prevalence of macular edema reinforces current observations and supports a role for ophthalmic monitoring during fingolimod use.

References:

Key Words: multiple sclerosis, optical coherence tomography, macula, edema, fingolimod

Financial Disclosure: Dr. Calabresi has received personal compensation for consulting and serving on scientific advisory boards from; Biogen-IDEC, Teva, Genzyme, Vaccinex, and Novartis; and has received research funding from companies Biogen-IDEC, Teva, EMD Serono, Vertex, Genentech, Abbott, and Bayer. The remaining authors had no disclosures.
Macular Thickness Measurements with Optical Coherence Tomography for Quantification of Axonal loss in Chronic Papilledema from Pseudotumor Cerebri Syndrome

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Introduction:
To evaluate the ability of Fourier-domain optical coherence tomography (FD-OCT) macular thickness parameters to differentiate between eyes with chronic papilledema and healthy eyes and to investigate the relationship of such parameters with visual field (VF) loss assessed on standard automated perimetry (SAP).

Methods:
Fifty-eight eyes from 31 patients with chronic papilledema from pseudotumor cerebri syndrome and 78 eyes from 39 normals underwent FD-OCT (3D OCT-1000®, Topcon) examinations and ophthalmic evaluation including SAP. All patients had been submitted to previous treatment of the condition and had resolved papilledema. Macular thickness measurements were determined in both groups. Comparisons were made using Generalized Estimated Equations. Correlations between OCT and VF measurements were also verified.

Results:
In eyes with papilledema macular thickness parameters (mean ± SD) corresponding to the superior, temporal, inferior and nasal, inner and outer segments in papilledema eyes were: 283.5 ± 24.2; 271.1 ± 19.4; 282.0 ± 23.0; 284.6 ± 26.2; 245.2 ± 16.9; 231.4 ± 13.1; 238.2 ± 18.6 and 257.2 ± 24.5, respectively. Average macular thickness was 258.7 ± 18.3. Corresponding values from normal eyes were: 295.1 ± 18.8; 281.5 ± 15.5; 289.9 ± 17.0; 298.2 ± 16.3; 256.2 ± 15.2; 240.8 ± 13.3; 250.8 ± 16.2 and 275.9 ± 15.5. Average macular thickness measurement was 270.8 ± 12.9. Macular and RNFL thickness parameters were significantly reduced in papilledema eyes compared to normals. Macular thickness measurements were strongly correlated with VF sensitivity loss assessed with SAP.

Conclusion:
Eyes with chronic papilledema show significant thinning of the retinal thickness on the macular area, which is associated with the severity of visual field damage in these eyes. Macular thickness measurements could potentially be used to evaluate the amount of ganglion cell loss in patients with papilledema from pseudotumor cerebri syndrome.

References: None

Key Words: Optical coherence tomography, papilledema, pseudotumor cerebri syndrome, retinal axonal loss

Financial Disclosure: The authors had no disclosures.
Tuesday, February 14, 2012, 10:15 a.m. – 10:30 a.m.

Contrast Sensitivity Visual Acuity Is Deficient In Parkinson’s Disease And Degrades Multiple Aspects Of Motor Performance Under Conditions Of Dim Illumination

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Introduction:
To determine the effect of deficient contrast sensitivity visual acuity on gait performance since injurious falls in Parkinson Disease are a major healthcare concern and cost.

Methods:
Fifty one Parkinson’s subjects (Stage I-III H and Y) versus thirty controls. Tests included UPDRS scores, directive & contrast sensitivity binocular visual acuities using SLOAN wall charts tested at 100%, 2.5%, and 1.25%, as well as gait analysis (GaitRite) under conditions of high and low illumination (>80 & <4 candela). Gait measurements included: functional ambulation profile (FAP), step number, velocity, normalized velocity, step length, step length differential, stride length, & cadence. Exclusion criteria: VA <20/50, known night blindness, heart disease, known co-morbid neurologic or vestibular dysfunction.

Results:
Compared with controls, there was significantly poorer contrast visual acuity in the Parkinson’s group at 2.5% and 1.25% visual efficiency, an observation we have previously reported1. Further, such visual deficiency significantly degraded motor performance when compared to controls. In high illumination, PD subjects had a statistically significant difference in step cadence only. In dim illumination, PD subjects displayed poorer performances in FAP, velocity, normalized velocity, cadence, step length, and stride length.

Conclusion:
This study confirms the presence of contrast sensitivity deficits that significantly degrade motor performance in Parkinsonism under conditions of low illumination, presumably the result of retinal dopamine deficiency2, associated with inner retinal layer thinning3. Substandard FAP scores are particularly meaningful as there is high correlation between low FAP scoring and increased fall risk4. It appears that balance maintenance is affected even in early stages of Parkinsonism. It seems plausible that detection of defects in low contrast visual settings may aid in reduction of falls risk. Further study is required to determine if identification of low contrast sensitivity defects may serve as a premotoric marker for Parkinsonism.

References:

Key Words: Parkinson, Contrast Sensitivity, Balance Maintenance, Gait Performance, Motor Performance

Financial Disclosure: The authors had no disclosures.
Tuesday, February 14, 2012, 10:30 a.m. – 10:45 a.m.

Effects of Induced Monocular Blur versus Anisometropic Amblyopia on Saccadic Eye Movements

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Introduction:
Anisometropic amblyopia is a visual impairment of one eye due to a significant difference in refractive error between the eyes. Patients with anisometropic amblyopia have prolonged and more variable saccade latency. We investigated whether the prolonged saccade latency is due to a loss of visual acuity alone, or due to a unique effect of amblyopia as a result of abnormal visual development during early childhood.

Methods:
Twelve patients with anisometropic amblyopia and 12 visually-normal participants were tested. Participants executed saccades to targets presented randomly at ±5° and ±10° on a computer screen during binocular and monocular viewing (fellow eye / amblyopic eye for patients, right / left eye for control subjects). Control subjects were tested before, immediately after, and 5 hours after artificially-induced monocular blur (to 20/50) using a plus contact lens. Latency, amplitude, and peak velocity of primary saccades were analyzed.

Results:
Patients with amblyopia had significantly longer (p=0.006) and more variable (p=0.037) saccade latency during amblyopic eye viewing (221±67 ms), compared to fellow eye (185±29 ms) or binocular viewing (189±52 ms). In contrast, induced monocular blur did not affect saccade latency or variability: normal vision (binocular: 169±29 ms; monocular left: 186±30 ms; monocular right: 193±32 ms), immediately after induced blur (binocular: 172±31 ms; normal acuity eye: 185±29 ms; blurred eye: 189±31 ms) and 5 hours after induced blur (binocular: 177±32 ms; normal acuity eye: 193±35 ms; blurred eye: 191±33 ms).

Conclusion:
Patients with amblyopia demonstrated significantly longer and more variable saccade latency during amblyopic eye viewing. This observation was not reproduced after artificially-induced monocular blur in visually normal subjects, suggesting that a loss of visual acuity alone could not explain the saccadic deficits seen in amblyopia.

References: None

Key Words: Amblyopia, Saccades, Induced Blur

Financial Disclosure: The authors had no disclosures.
Tuesday, February 14, 2012, 10:45 a.m. – 11:00 a.m.

Idiopathic Intracranial Hypertension Treatment Trial (IIHTT) Update

Michael Wall (on behalf of the IIHTT Study Group)

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Introduction:
The Neuro-Ophthalmology Research Disease Consortium (NORDIC) has developed the IIHTT. This trial, funded by the NIH, has half of its 154 subjects enrolled. The clinical trial tests the hypothesis, in patients with mild visual loss, that treatment of IIH with diet and acetazolamide is superior to treatment with diet and placebo. A maximum tolerated dosage of acetazolamide is used, up to 4 grams per day. A second aim of the trial attempts to uncover the cause of IIH.

Methods:
Forty-five sites are enrolling subjects in this randomized double masked, placebo controlled study. To enter the trial, subjects need to be age 18-60, have a mean deviation on automated perimetry of between -2 and -7 dB and meet the modified Dandy criteria for IIH. The primary outcome variable is the six-month change in mean deviation using SITA standard 24-2 testing. Secondary outcome measures are change in Frisen fundus photo grade, change in CSF pressure, other perimetry outcomes and various quality of life measures. Single nucleotide polymorphisms will be studied to identify biomarkers important in the pathogenesis of IIH in study subjects and matched controls. A spectral OCT substudy is in progress at 27 sites. Participants will continue to be followed in an observational phase for up to 4 years.

Results:
Seventy-six women and one man have enrolled. Their ages range from 18-48 with a mean of 29.9; 54% are white and 28% black; 14% are Hispanic/Latino; 73% had transient visual obscurations; 66% had pulse-synchronous tinnitus; 53% reported visual loss; 49% had photophobia; and 40% reported radicular pain. Cross sectional analyses at baseline of vitamin A metabolism measuring retinol, ATRA, alpha-tocopherol, gamma-tocopherol, beta-carotene, alpha-carotene, cryptoxanthin, beta-cryptoxanthin, CSF Retinol and CSF ATRA show no differences between IIH patients and control subjects.

Conclusion:
The IIHTT is at its mid-point in recruitment and is progressing well. We anticipate completing enrollment by the end of 2012. Forty-five NORDIC sites are functioning and available for additional investigations.

References: None

Key Words: idiopathic intracranial hypertension, papilledema, clinical trials

Financial Disclosure: The authors had no disclosures.
Single motor unit recordings of ocular vestibular evoked myogenic potentials in human extraocular muscles

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Introduction:
The ocular vestibular evoked myogenic potential (oVEMP) is a vestibular-dependent reflex and clinical test of otolith function measured from the extraocular muscles with surface electrodes. Since it is not known exactly which muscles contribute to the reflex, we wished to determine the muscle of origin of the oVEMP and investigate the neural pathway of the vestibulo-ocular reflex (VOR) to individual eye muscles.

Methods:
Three healthy subjects were stimulated with 500Hz, 4ms bursts of vibration and sound. Motor units from the inferior oblique (IO) and inferior rectus (IR) eye muscles were recorded with concentric needle electrodes. Standard oVEMPs were recorded simultaneously with surface electrodes placed below the eyes. Single motor units were extracted from multi-unit recordings and quantified in peri-stimulus histograms.

Results:
Following vibration, an initial increase in IO single motor unit discharge was measured at a mean peak latency of 11.0ms (range 10-13ms, n=6 units). Discharge was up to 10 times baseline level during the pre-stimulus period. The initial peak was followed by subsequent troughs and peaks at intervals of ~5ms. In the IR muscle, a similar pattern of alternating excitation and inhibition was seen, but was delayed by ~5ms compared to the IO muscle. Following sound stimulation, an increase in IO activity was seen in the muscle contralateral to the stimulus at a mean latency of 13.8ms. The latency and polarity of the simultaneous surface oVEMP were similar to the IO needle recordings.

Conclusion:
The study identifies excitation of the IO as the source of the initial oVEMP signal in response to vibration and sound. Its vertical antagonist, the IR, shows delayed excitation by ~5ms but does not contribute to the initial response. These muscles show reciprocal activation, consistent with their role as vertical antagonists. Single motor unit recordings in human extraocular muscles demonstrate the contribution of individual muscles to the VOR.

References: None

Key Words: extraocular muscle, electromyography, ocular vestibular evoked myogenic potential (oVEMP), vestibulo-ocular reflex (VOR), single motor unit

Financial Disclosure: The authors had no disclosures.
A murine model of giant cell arteritis: Infection with a Burkholderia pseudomallei-like strain treated with steroids and antibiotics

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Introduction:
At NANOS 2011, we presented data demonstrating a strong association between a strain of Burkholderia similar to B. pseudomallei and giant cell arteritis (GCA). Since then, we have isolated, cultured and characterized this strain. We found this strain to be sensitive to minocycline in vitro. To better understand the pathogenesis of human infection, we infected mice with this Burkholderia pseudomallei-like strain.

Methods:
24 mice received intraperitoneal injection of these bacteria. 6 mice received steroids+minocycline, 6 mice received steroids alone, 6 mice received minocycline alone, and 6 mice received no therapy. Kaplan-Meier curves of survival were plotted over 30 hours.

Results:
The mice receiving no therapy quickly became sick and half were dead 30 hours after injection with the bacteria. Four of the mice that received minocycline alone were still alive at 30 hours. Five of the mice that received steroids alone were still alive at 30 hours. All 6 mice that received steroids+minocycline were still alive at 30 hours. Histologic sections taken from mice that did not receive treatment showed widespread infection, including liver, lung and spleen. Bacterial burden was significantly reduced in the tissues of animals that had received minocycline alone. Bacterial burden was not significantly reduced in the tissues of animals that had received steroids alone. Sections taken from lung showed lymphocytic infiltration of blood vessels (vasculitis) and bronchioles (bronchiolitis).

Conclusion:
If this B pseudomallei-like strain is indeed the cause of GCA, this model may explain why steroids are an effective treatment in humans. These results indicate that the immune response to infection with this strain may be more damaging to the host than the bacterial infection itself. These results indicate that it may be unwise to attempt a clinical trial of antibiotics alone to treat GCA. Instead, a trial comparing steroids+antibiotics should be compared to steroids+placebo.

References: None

Key Words: giant cell arteritis, temporal arteritis, Burkholderia

Financial Disclosure: The authors had no disclosures
Tuesday, February 14, 2012, 11:30 a.m. – 11:45 a.m.

Treatment of Subjects with Giant Cell Arteritis with Antibiotics.

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Introduction:
At NANOS 2011 we presented data establishing an association between a *Burkholderia pseudomallei-like* strain and giant cell arteritis (GCA). This strain is sensitive to minocycline and doxycycline. We are treating a cohort of GCA patients with antibiotics as adjunct therapy to a standard taper of prednisone to determine if antibiotic treatment lowers serum LPS levels and prevents relapse of the disease.

Methods:
Six patients were enrolled. All fulfilled the 1990 American College of Rheumatology criteria for GCA. Five were temporal artery biopsy proven while one lacked temporal artery inflammation. Subjects underwent monthly evaluations to monitor for signs and symptoms of relapse. ESR, CRP, and platelet counts, as well an ELISA for *B. pseudomallei-like* LPS were evaluated at various intervals.

Results:
The mean ages of the 6 subjects was 80 (range 69-88 years). Three of the patients were male. All subjects experienced at least one neuro-ophthalmologic manifestation. Three subjects were newly diagnosed while three were established patients experiencing a relapse of their disease. All subjects had positive ELISA tests for the organism. Five subjects were treated with oral minocycline 100 mg BID for one month; one subject was treated with oral doxycycline, 100 mg BID for 2 months. All subjects followed a standard prednisone taper. All subjects showed reduced serum levels LPS between 4 and 8 weeks after the start of antibiotic therapy. No adverse events related to antibiotic therapy were recorded. At the time of chart review, no subjects suffered a relapse of their disease and all subjects have continued to taper off steroids.

Conclusion:
Minocycline and doxycycline appear to be effective in reducing serum LPS levels of the *B. pseudomallei-like* infection. Although these data appear promising, a controlled clinical trial of larger number of patients will be required to determine if antibiotic treatment is an effective adjuvant in the treatment of GCA.

References: None

Key Words: giant cell arteritis, temporal arteritis, Burkholderia

Financial Disclosure: The authors had no disclosures.
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**Distinguishing Retinal Nerve Fiber Layer Injury by Optical Imaging in Acute Optic Nerve Head Swelling**

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**Introduction:**
Retinal nerve fiber layer (RNFL) thickening, but not acute axonal injury, is readily demonstrated by OCT in optic nerve head swelling (ONH). Since scanning laser polarimetry (SLP) measures RNFL by polarizing features of intact axons, combining both methods might reveal differing mechanisms within RNFL swelling.

**Methods:**
We prospectively studied OCT and SLP in eyes with ONH swelling due to new optic neuritis (ON) and NAION. We defined swelling as having average RNFL by OCT > 95th percentile of controls at presentation. Regional RNFL thinning was defined by having an RNFL quadrant value < 5th percentile of controls. Each eye had vision testing and imaged at intervals up to 6 months.

**Results:**
At presentation, the mean average RNFL by OCT was 208 µm in 21 eyes with NAION and 143 µm in 13 eyes with ON (p = 0.003). In contrast, the average RNFL by SLP was less for NAION than for ON eyes (p = 0.02). By SLP, RNFL was reduced in 1 ON eye, and in 13 NAION eyes, with the superior quadrant affected most (52 µm for NAION, 74 µm for ON). In NAION eyes, quadrants with retardation reduction had related visual field loss that did not recover and had RNFL loss by OCT in the same quadrants at 6 months. At 1 month the RNFL was thinned by OCT in 7/17 and by SLP in 14/16 NAION eyes compared with ON eyes by SLP (1/11; p = 0.0004) or by OCT (0/11; p = 0.006).

**Conclusion:**
OCT and SLP reveal different RNFL changes with ONH swelling. OCT shows RNFL thickening, due to intra-axonal and interstitial edema. SLP shows decreased retardance with axonal injury associated with visual field loss, unlikely to recover.

**References:** None

**Key Words:** optical imaging, NAION, optic neuritis, scanning laser polarimetry, OCT

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