PLATFORM SESSION I

Monday, February 29, 2016 ● 5:00 pm - 7:00 pm

Moderators: Rudrani Banik, MD and Marc Dinkin, MD

5:00 pm - 5:15 pm
Laura Balcer
Efficacy for Remyelination and Safety of Anti-LINGO-1 Monoclonal Antibody (BIIB033) in Acute Optic Neuritis: Results from the RENEW Study

5:15 pm - 5:30 pm
Michael Wall
The Idiopathic Intracranial Hypertension Treatment Trial: Outcomes from Months 6-12

5:30 pm - 5:45 pm
Jason H. Peragallo
The Relationship of Vision and Quality of Life (QOL) in Patients with Pediatric Primary Brain Tumors (PBT)

5:45 pm - 6:00 pm
Gregory P. Van Stavern
Pupillary Light Reaction in Pre-Clinical Alzheimer's Disease vs. Normal Aging Controls

6:00 pm - 6:15 pm
Konrad P. Weber
A New Complementary Video Head Impulse Test Paradigm to Elicit Anti-Compensatory Saccades as an Indicator of Peripheral Vestibular Function

6:15 pm - 6:30 pm
Patrick A. Sibony
En Face and Raster SD-OCT Imaging of Retinal and Choroidal Folds in Papilledema

6:30 pm - 6:45 pm
Michael D. Richards
Abnormal Integration of Audiovisual Spatial Information in Amblyopia

6:45 pm - 7:00 pm
Robert A. Avery
Quantitative MRI Criteria for Optic Pathway Enlargement in Children with Neurofibromatosis Type 1

*Please note that all abstracts are published as submitted.*
Monday, February 29, 5:00 - 5:15 pm
Efficacy for Remyelination and Safety of Anti-LINGO-1 Monoclonal Antibody (BIIB033) in Acute Optic Neuritis: Results from the RENEW Study

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Introduction:
Anti-LINGO-1 is a monoclonal antibody antagonist of LINGO-1, an oligodendrocyte differentiation and myelination suppressor. RENEW (NCT01721161) aimed to determine the efficacy and safety of anti-LINGO-1 for CNS remyelination.

Methods:
Subjects with a first unilateral acute optic neuritis episode were treated with high-dose steroids and randomized to 100 mg/kg anti-LINGO-1 IV or placebo every 4 weeks. Nerve conduction latency recovery using full-field visual evoked potential (FF-VEP) in the affected eye over time versus unaffected eye at baseline was used to assess remyelination (pre-specified primary endpoint). Retinal neuroprotection was studied by measuring the thickness of the retinal nerve fiber and ganglion cell layers using spectral-domain optical coherence tomography (SD-OCT) and change in low-contrast letter acuity (LCLA). Patient-reported outcomes (PRO) were also assessed. Between-treatment comparisons were evaluated by ANCOVA and mixed-effect model repeated measure in subjects who completed the study and did not miss >1 study dose or receive MS modifying therapy (pre-specified per-protocol population; n=69/82 subjects randomized). Safety/tolerability were evaluated in those who received ≥1 study dose and included adverse event (AE) and clinical laboratory result assessments.

Results:
Anti-LINGO-1-treated subjects (n=33) showed improved FF-VEP latency recovery versus placebo (n=36): mean (95% confidence interval) −7.55 ms (−15.12 to 0.01) at Week 24 (P=0.05); −9.13 ms (−16.11 to −2.14; P=0.01) at Week 32. 54% of anti-LINGO-1 subjects had normal/near normal latency at Week 24 (affected eye FF-VEP latency ≤10% worse than the fellow eye) versus 27% of the placebo group (P=0.04). Additional subgroup analyses and PRO data will be presented. No treatment differences were observed in SD-OCT and LCLA. 34/41 in each group experienced any AE, serious AEs (SAE) occurred in 2 placebo and 5 anti-LINGO-1 subjects, with treatment-related SAEs reported in 3 subjects.

Conclusions:
Improvement in FF-VEP latency is consistent with the first evidence of remyelination in a Phase 2 trial. Anti-LINGO-1 was generally well tolerated.

References: None

Keywords: Optic Nerve Trauma And Treatment, Visual Fields, Demyelinating Disease, Neuro-Ophtl & Systemic Disease, Optic Neuropathy

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Monday, February 29, 5:15 - 5:30 pm
The Idiopathic Intracranial Hypertension Treatment Trial: Outcomes from Months 6 - 12

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Introduction:
Our goal was to determine whether the beneficial effects of acetazolamide (ACZ) in improving vision continues from months 6 to 12 in participants of the Idiopathic Intracranial Hypertension Treatment Trial (IIHTT).

Methods:
In the IIHTT, after 6 months of a weight management program and either placebo or maximally tolerated ACZ, subjects transitioned from study drug to ACZ unless their papilledema resolved. The main outcome was the change in MD from Month 6 to Month 12 in the study eye, groups based on treatment at study entry and after 6 mos. – 1) ACZ to ACZ n = 34, 2) placebo to ACZ n = 35, 3) ACZ to no treatment n = 20, and 4) placebo to no treatment n = 12.

Results:
The placebo subjects in group 4 improved 0.86 dB, p = 0.04 at 12 mos. The other three groups improved 0.35 to 0.41 dB PMD. Mean improvements in papilledema grade also occurred in all groups but most markedly in the group that exchanged placebo for ACZ (0.91 Frisén grade units, p <0.001). QoL scores and headache disability, improved also with a large and significant improvement in the group that transitioned from placebo to ACZ. Significant weight change occurred in those transitioning from placebo to ACZ who lost about 6 pounds (p = 0.02) while those tapered off acetazolamide gained about 6 pounds (p = 0.03).

Conclusions:
Improvements in MD continued from month 6 to month 12 of the IIHTT in all treatment groups. This effect was most marked and significant in the placebo group tapered off study drug. Significantly beneficial effects of ACZ on papilledema grade and QoL increased from month 6 to 12. Adding ACZ to the placebo group subjects significantly improved their quality of life.

References:

Keywords: Idiopathic Intracranial Hypertension, Perimetry, Visual Fields

Financial Disclosures: The authors had no disclosures.

Grant Support: None.
Monday, February 29, 5:30 - 5:45 pm
The Relationship of Vision and Quality of Life (QOL) in Patients with Pediatric Primary Brain Tumors (PBT)

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Introduction:
Brain tumors are the leading cause of death from childhood cancer. Overall survival has improved due to earlier detection, better therapies, and improved surveillance. Permanent sequelae of the tumor and its treatment may cause severe impairment and decreased QOL. Visual dysfunction and impaired vision-related QOL (VR-QOL) are often not recognized in children because of examination difficulty and lack of awareness.

Methods:
We evaluated visual impairment and its effects on QOL in an ongoing quality improvement project. Patients ≤18 yo, ≥6 months from diagnosis of primary brain tumor, excluding primary intrinsic anterior visual pathway tumors, underwent neuro-ophthalmologic examination. Health-related QOL (HR-QOL) questionnaires, using PedsQL Brain Tumor Module,2 were obtained from patients and parents. VR-QOL questionnaires, using CVFQ (Children’s visual function questionnaire)3 in children <8yo, and EYE-Q4 in children 8-18yo, were obtained. Demographic data, driving status, schooling, and use of low-vision aids were recorded.

Results:
43 patients were evaluated. Astrocytomas (9/43) and craniopharyngiomas (9/43) were the most common tumors. Diagnosis was made at 6.6 years (range 0.2-17), Mean age at examination was 11.7 years (IQ range 8.8-15.6). 3/43 patients (7%) were legally blind; 12/43(28%) were visually impaired. Eye-Q median score was 4.275(IQ range 3.925-4.750). Eye-Q score decreased 0.14 with every 0.1 increase in logMAR visual acuity [p<0.001]. Average Eye-Q score for legally blind patients was 1.4; for non-legally blind patients 4.35[p=0.003]. Cognitive HR-QOL scores decreased 1.2 for every 0.1 increase in logMAR visual acuity [p=0.06].

Conclusions:
Pediatric PBT patients’ vision, HR-QOL, and VR-QOL are often severely affected, even when the PBT is considered "cured“. Visual acuity is correlated with VR-QOL. Number of treatment modalities used was not associated with lower QOL. Systematic neuro-ophthalmologic examinations in pediatric PBT patients may improve long-term visual outcomes and QOL through earlier interventions.

References:
2. www.pedsql.org/

Keywords: Tumors, Pediatric Neuro-Ophthalmology

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Grant Support: None.
Pupillary Light Reaction in Pre-Clinical Alzheimer’s Disease vs. Normal Aging Controls

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Introduction:
Alzheimer’s disease (AD) is a neurodegenerative disease characterized by cognitive deficits and visual dysfunction. Neural biomarkers such as PET-Pib imaging and CSF ABeta levels are predictive of future development of AD but are expensive and cumbersome. There is increasing interest in using ocular biomarkers as a surrogate for disease activity in AD. Several studies have shown that the pupillary light response (PLR) can differentiate AD patients from healthy controls. However, many of these studies assessed the PLR in established AD, and failed to control for systemic diseases and medications which affect the PLR. The PLR in pre-clinical AD remains poorly studied.

Methods:
Subjects were recruited from our institution’s Alzheimer’s Disease Research Center. All subjects completed PET-Pib imaging, cerebrospinal fluid analysis and at least 1 neuropsychiatric assessment and had clinical dementia rating (CDR) of 0. Subjects were divided into a biomarker + and – group. Subjects with systemic disease or drugs known to affect the PLR were excluded. Pupillometry was performed by using the NeurOptics PLR-200 Pupillometer.

Results:
59 participants were recruited, 24 biomarker + and 35 biomarker-. All PLR parameters were assessed. Comparisons between groups were analyzed using SAS V9.3. Subjects + for ABeta had significantly reduced constriction percentage compared with ABeta – subjects, p= 0.03. None of the other pupillometry parameters showed a significant difference between groups. Males showed reduced maximal constriction (p=0.03) and reduced average constriction velocity (p=0.007) compared with females.

Conclusions:
Constriction percentage was significantly reduced in the ABeta+ group compared with the ABeta-, but no other significant differences were found. This suggests that reduced cholinergic tone may alter the PLR in pre-clinical AD, but this effect may be small at the earliest stages of the disease. We found significant gender differences in PLR in the biomarker + and – groups.

References: None.

Keywords: Pupillometry, Alzheimer’s Disease, Ocular Biomarkers

Financial Disclosures: The authors had no disclosures.

A New Complementary Video Head Impulse Test Paradigm to Elicit Anti-Compensatory Saccades as an Indicator of Peripheral Vestibular Function

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Introduction:
The conventional head impulse test paradigm (HIMP) elicits catch-up saccades as a sign of vestibular loss. The new suppression head impulse paradigm (SHIMP) is designed to elicit catch-up saccades as an indicator of vestibular function. During this new complementary paradigm, the subject is asked to follow a head-fixed target, which is rotating with the head, rather than to fixate an earth-fixed target as in HIMP.

Methods:
The saccadic patterns in response to the SHIMP and HIMP paradigms, as well as the gain of the vestibulo-ocular reflex (VOR) were quantified with the video head impulse test (vHIT). Five patients with unilateral vestibular loss (UVL) and five patients with bilateral vestibular loss (BVL) were compared to six normal subjects.

Results:
VOR gains correlated closely ($R^2=0.97$) with slightly lower SHIMP than HIMP gains (mean gain difference $0.06±0.05$ SD, $p<0.001$). However, the resulting catch-up saccade patterns in the two paradigms were complementary: While HIMP elicited compensatory saccades mainly in patients, SHIMP elicited anti-compensatory saccades in normals, but only few in BVL patients. To the affected side UVL patients produced mostly covert saccades during HIMP, but mainly overt saccades during SHIMP.

Conclusions:
The new SHIMP paradigm produced closely correlating VOR gains with slight, but significant VOR suppression compared to SHIMP. While the appearance of compensatory saccades during conventional HIMP indicates vestibular loss, the anti-compensatory saccades during SHIMP indicate vestibular function. In UVL patients SHIMP elicits mainly overt saccades to the affected side, thus facilitating VOR gain measurements. The new complementary SHIMP paradigm is equally simple to explain to patients as the HIMP paradigm, while the results are complementary.

References:

Keywords: Diagnostic Tests, Ocular Manifestations Of Vestibular Disorders, Vestibular, Video Head Impulse Test, Vestibulo-Ocular Reflex

Financial Disclosures: GMH, ISC, HGM, LAM, KPW act as unpaid consultants and have received funding for travel and free equipment for beta testing from GN Otometrics. However, the study was conducted with a custom-built, non-commercial prototype and the authors have no commercial interest in video head impulse systems. LM, SJR and AMB report no disclosures.

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**Monday, February 29, 6:15 - 6:30 pm**

*En Face and Raster SD-OCT Imaging of Retinal and Choroidal Folds in Papilledema*

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**Introduction:**
The purpose of this study was to demonstrate how *en face*/raster SD-OCT imaging of the optic disc and retina in papilledema can be used to detect and characterize the patterns of folds and wrinkles in papilledema.

**Methods:**
Masked reviewers evaluated 125 patients with papilledema from the IIH Treatment Trial (IIHTT). We compared the relative sensitivity of *en face*/raster SD-OCT to fundus photographs in identifying retinal and choroidal folds at baseline. Using a standardized protocol, folds were characterized by type, frequency, location, pattern and spatial wavelength. The relationship between the presence and types of folds and a number of structural and functional parameters were examined.

**Results:**
We identified several types of folds: peripapillary wrinkles (PPW), retinal folds (RF), choroidal folds (CF). SD-OCT was more sensitive than fundus photos in identifying folds. The frequency, with photos was 26%, 19%, and 1% respectively; with SD-OCT was 46%, 47%, and 10%. At least one type of fold was present in 41% of eyes with photos and 73% with SD-OCT. Each type of fold has a distinctive pattern, location and spatial wavelength that reflects the biomechanical stress and strain, material (tissue layer) properties and structural geometry of the optic nerve head (ONH) and retina. Parameters that reflect the severity of papilledema (e.g., RNFL, disc volume, Frisen scale) were associated with PPW/RF whereas anterior deformation in the shape of the eye-wall was associated with CF/RF. These associations were statistically significant. Folds were not associated with baseline vision.

**Conclusions:**
The interactive features of the SD-OCT using *en face* and raster imaging enhances our ability to identify and characterize folds compared to fundus photos. Retinal and choroidal folds are common in papilledema. Folds in papilledema are the biomechanical expressions of stress/strain on the ONH and load-bearing structures (sclera, lamina) induced by intracranial hypertension; they are products of a complex interaction between the degree of papilledema and anterior deformation of the load-bearing structures.

**References:**

**Keywords:** OCT, Papilledema, Choroidal Retinal Folds, Optic Nerve, Intracranial Hypertension

**Financial Disclosures:** The authors had no disclosures.

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Abnormal Integration of Audiovisual Spatial Information in Amblyopia

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Introduction:
Perception of our environment involves combining information from multiple senses by a process termed multisensory integration. This process is evident in illusions like the McGurk effect, which juxtapose subtly incongruous auditory and visual stimuli to reveal the bias in the neurological networks underlying perception. Interestingly, studies using the McGurk effect show that patients with unilateral amblyopia integrate auditory and visual speech information in an abnormal way. It is unknown, however, whether this abnormality is specific to speech, or whether it reflects a more general failure of multisensory integration in amblyopia. To address this question, we used another illusion – the ventriloquism effect – to examine integration of non-speech audiovisual information. The ventriloquism effect is known to obey the maximum likelihood estimate (MLE) model of optimal combination in normal adults, and thus provides a predictive model to evaluate performance in amblyopia.

Methods:
All experiments were done in an acoustic chamber under binocular viewing conditions. Adults with amblyopia (n=8) and normal controls (n=17) performed spatial localization of auditory clicks, visual Gaussian blobs (5 sizes), and combined audiovisual stimuli in a 2-alternative forced choice paradigm. Localization precision and bias for each click, blob, and click-blob pair was estimated from the fitted psychometric functions. Performance was compared to predictions from the MLE model.

Results:
Unlike normal controls, patients with unilateral amblyopia did not combine auditory and visual information as predicted by the MLE model when viewing binocularly (p = 0.003). Auditory spatial information was over-valued in amblyopia.

Conclusions:
Integration of audiovisual spatial information in amblyopia does not obey the MLE model of optimal combination. This suggests that normal visual experience may be required for the development of robust audiovisual integration, and points to a lifelong impact of pediatric sensory disturbances on perception.

References: None.

Keywords: Amblyopia, Multisensory Integration, Higher Visual Functions, Psychophysics

Financial Disclosures: The authors had no disclosures.

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Quantitative MRI Criteria for Optic Pathway Enlargement in Children with Neurofibromatosis Type 1

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Introduction:
Children with Neurofibromatosis type 1 (NF1) frequently develop optic pathway gliomas (OPGs), low grade tumors of the anterior visual pathway (AVP) which include the optic nerve, chiasm and tract. The diagnosis of an OPG is frequently based upon enlargement of these structures, yet a quantitative MRI criterion of enlargement does not exist. We introduce quantitative size thresholds for enlargement of the AVP.

Methods:
Children 0.3-18.6 years of age who underwent high resolution T1-weighted cube MRI and did not have other acquired, systemic or genetic conditions (other than NF1) that could alter their AVP, were eligible for inclusion. Diameter, volume and length of AVP structures were calculated from reconstructed MRI images. Values above the 95th percentile from the control subjects were considered the threshold for defining an abnormally large AVP measure.

Results:
One-hundred eighty-six children (controls = 82; NF1noOPG = 54; NF1+OPG = 50) met inclusion criteria. NF1noOPG and NF1+OPG subjects demonstrated greater maximum optic nerve diameter and volume, optic chiasm volume and total brain volume compared to controls (P <0.05, all comparisons). Total brain volume, rather than age, predicted optic nerve and chiasm volume in controls (P <0.05). Applying the 95th percentile threshold to all NF1 subjects, the maximum optic nerve diameter (4.0 mm) and AVP volumes resulted in few false positive errors (specificity >80%, all comparisons).

Conclusions:
Quantitative reference values for AVP enlargement will enhance development of objective diagnostic criteria for OPGs secondary to NF1.

References: None.

Keywords: Neuroimaging, Tumors, Pediatric Neuro-Ophthalmology

Financial Disclosures: The authors had no disclosures.