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Shalini V. Mohan, MD  
Unopposed Immune Stimulation in Giant Cell Arteritis (GCA): A Consequence of a Reprogrammed STAT1 Signaling Pathway

5:15 p.m. - 5:30 p.m.  
Jonathan C. Horton, MD, PhD  
Cortical Metabolic Activity Matches the Pattern of Visual Suppression in Strabismus

5:30 p.m. - 5:45 p.m.  
Ali S. Saber Tehrani, MD  
Quantitative Video-Oculography for Diagnosing Stroke at the Bedside in Acute Vertigo: An “ECG” for the Eyes

5:45 p.m. - 6:00 p.m.  
Fiona Costello, MD, FRCP  
Exploring the Temporal Evolution of Structural and Functional Changes after Acute Optic Neuritis

6:00 p.m. - 6:15 p.m.  
Y. Joyce Liao, MD, PhD  
TrkB Neurotrophin Receptor Activation with Pharmacophore as Possible Treatment for Anterior Ischemic Optic Neuropathy

6:15 p.m. - 6:30 p.m.  
Michael E. Ward, MD, PhD  
Progranulin Deficiency Causes TDP43 Mislocalization and Neuron Death in the Retina

6:30 p.m. - 6:45 p.m.  
Daniel Rappoport, MD  
Intravitreal Injection Of Bevacizumab May Be Neuroprotective In A Mouse Model Of Optic Nerve Crush

6:45 p.m. - 7:00 p.m.  
Brian Goldhagen, MD  
Subclinical Optic and Retinal Atrophy in Eyes with Papilledema detected by OCT
Monday, February 11, 5:00 - 5:15 p.m.

Unopposed Immune Stimulation in Giant Cell Arteritis (GCA): A Consequence of a Reprogrammed STAT1 Signaling Pathway

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Introduction:
GCA can manifest with severe vision loss from involvement of the ophthalmic artery or its branches. Arteritis is caused by unopposed activation of CD4+ T cells and persistent cytokine production (e.g. IL-6). In healthy immune responses, early innate cytokines (e.g. IFN-γ) drive feed-forward amplification loops but also promote anti-inflammatory T-regulatory cells (T_{reg}) to contract and terminate immune reactions. We have studied whether such critical immune regulatory pathways are maintained in GCA.

Methods:
We have evaluated the distribution of CD4+ T cells subsets and STAT1 pathway activation by multi-parameter flow cytometry in patients with biopsy-proven GCA (n = 51) and age-matched healthy controls (n = 56). We probe cytokine-induced immune modulation through IFN-α stimulation of CD4+ T cells, which leads to phosphorylation of the signaling molecule STAT1 and induction of STAT1 target genes.

Results:
Compared to controls, GCA patients have relatively well-maintained naïve CD4+ T cells, but more of their memory T cells are chronically stimulated. This immune activation is associated with a significantly lower level of T_{reg} cells in GCA patients (4.9% vs. 8.3%, p <0.0006). In healthy individuals, T_{reg} frequencies are highest in IFN-α high-responders. IFN-α responsiveness is significantly impaired in GCA as demonstrated by reduced concentrations of phosSTAT1 (mean fluorescence intensity 313 in GCA pts vs. 367 in controls, p = 0.01). IFN-α-induced gene transcript levels in resting and post-stimulation T cells confirm that patients exhibit a defective STAT1 signaling pathway.

Conclusions:
PhosSTAT1 levels, STAT1 target gene transcripts, and CD4+ T_{reg} cells are markedly reduced in GCA patients, indicating a defective STAT1-dependent immunoregulation. We propose that unrestrained immune activity in GCA is due to reprogramming of the STAT1 signaling pathway, weakening immune resolution via T_{reg} induction. Therapeutic approaches to GCA need to include measures to restore T_{reg} activity as a means to oppose immune stimulation and terminate inflammatory activity.

Keywords: Giant Cell Arteritis, Ischemic Optic Neuropathy, STAT1, CD4+ T cells, Regulatory T cells

Monday, February 11, 5:15 - 5:30 p.m.

Cortical Metabolic Activity Matches the Pattern of Visual Suppression in Strabismus

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Introduction:
When an eye becomes deviated in early childhood a person does not experience double vision. In alternating exotropia, the extra image is prevented from reaching perception by suppression of each eye’s peripheral temporal retina. To test the impact of suppression on neuronal activity in primary visual cortex, the pattern of cytochrome oxidase (CO) staining was examined in macaques raised with exotropia.

Methods:
Exotropia was induced in 4 macaques by disinserting the medial rectus muscles after birth. The monkeys never regained fusion because their eyes were misaligned throughout the critical period for binocular vision. When mature, tritiated proline was injected into the right eye to label the ocular dominance columns. Alternating sections from striate cortex were processed for CO or autoradiography.

Results:
CO staining showed no ocular dominance columns in opercular cortex, where the central visual field is represented, indicating that signals coming from the central retina in each eye were perceived. However, the border strips at the edges of ocular dominance columns appeared pale, reflecting a loss of activity in binocular cells from disruption of fusion. In calcarine cortex, where the peripheral visual field is represented, there were alternating pale and dark bands resembling ocular dominance columns. In the right calcarine cortex, the pale CO columns matched the labeled proline columns of the right eye. In the left calcarine cortex, the pale CO columns overlapped the unlabeled columns of the left eye.

Conclusions:
In each hemisphere, metabolic activity was reduced in the ipsilateral eye’s ocular dominance columns which serve the peripheral temporal retina. This finding is consistent with dichoptic visual field maps obtained in humans with alternating exotropia, which show suppression of the peripheral temporal retina in each eye. These data demonstrate a direct correlation between the layout of suppression scotomas in the visual fields of strabismic patients and the pattern of metabolic activity in the primary visual cortex.

References:


Keywords: Suppression, Strabismus, Exotropia, Cytochrome Oxidase, Dichoptic

Financial Disclosures: The authors had no disclosures.
Monday, February 11, 5:30 - 5:45 p.m.

Quantitative Video-Oculography for Diagnosing Stroke at the Bedside in Acute Vertigo: An “ECG” for the Eyes


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Introduction:
An estimated 250-500,000 patients present to US emergency departments annually with new, severe, persistent vertigo or dizziness. Roughly 70% have vestibular neuritis, but about 25% have posterior fossa strokes. Strokes can be distinguished from benign peripheral causes of AVS using three rapid bedside oculomotor tests (HINTS—Head Impulse test, Nystagmus, Test of Skew). The H.I.N.T.S. approach is more sensitive and less costly than MRI for acute stroke diagnosis in AVS, but requires expertise not routinely available. We sought to standardize the H.I.N.T.S. approach to stroke diagnosis in acute vestibular syndrome using a portable video-oculography device measuring oculomotor physiology in real time, conceptually similar to using electrocardiography (ECG) to diagnose myocardial infarction in chest pain.

Methods:
Prospective diagnostic accuracy study (08/2011–06/2012). Adult emergency department patients with AVS defined as new, persistent dizziness/vertigo, nystagmus, plus one or more of the following: (1) nausea/vomiting, (2) head motion intolerance, (3) new gait unsteadiness. We measured H.I.N.T.S. results including quantitative horizontal head impulse testing of vestibulo-ocular reflex function. Two masked vestibular experts rated oculomotor findings, which were compared to final diagnoses. Final diagnoses were considered “gold-standard” if masked neuroimaging raters agreed MRI brain with diffusion-weighted imaging (MRI-DWI) showed an acute stroke at any time or was negative >48 hours but <7 days after symptom-onset.

Results:
We identified 22 consecutive AVS patients and included 20. Mean age was 60 years (range 30-76) and 15 were men. All underwent MRI-DWI, 12 in the optimal time window. Expert-rated video-oculography-based H.I.N.T.S. exam was 100% accurate (10 strokes, 10 peripheral vestibular) relative to gold-standard neuroimaging diagnoses (n=12) or final expert clinical diagnoses (n=8).

Conclusions:
Device-based physiologic diagnosis of vertebrobasilar stroke in AVS appears possible. This bedside “eye ECG” approach, if validated, could fulfill a critical need for timely, accurate, efficient diagnosis in emergency department patients with dizziness and vertigo.

Keywords: Dizziness, Vertigo, Diagnosis, Diagnostic techniques, Neurological, Sensitivity and Specificity

Financial Disclosures: The authors had no disclosures.
Exploring the Temporal Evolution of Structural and Functional Changes after Acute Optic Neuritis

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Introduction:
Spectral-Domain OCT (SD-OCT) detects axonal loss [retinal nerve fiber layer thickness (RNFLT) thinning] and neuronal degeneration [macular volume (MV) loss] in optic neuritis (ON) and multiple sclerosis (MS) patients. SD-OCT has been proposed as an outcome measure in the ON Model of central nervous system inflammation. The purpose of this study was to determine the temporal evolution of functional and structural changes in retinal architecture after acute ON.

Methods:
In this prospective study, 50 ON patients underwent serial vision and SD-OCT testing within 30 days of symptom onset (baseline), 3-months, 6-months, and 12-months. Descriptive statistics were calculated for patient demographics. For analysis of correlated data, random effects mixed model was fitted to account for random effects of patient and follow-up time when determining the relationship between RNFLT and visual field mean deviation (VF) over time. To test potential predictors of change in RNFLT, multiple linear regression model was used.

Results:
The mean age of patients was 35.5 years (43 females). Mean RNFLT in ON eyes decreased from baseline [102.8 μm] to 3-months [85.3 μm] (p <0.05); from 3-months to 6-months [77.7 μm] (p <0.05); and from 6-months to 12-months [72.1 μm] (P <0.05). Similarly, MV values progressively decreased during follow up. Acutely, higher RNFLT corresponded to more severe vision loss, whereas during recovery, higher RNFLT was associated with better visual function. Male patients on average lost 35 μm more of RNFL thickness than female patients (p=0.05). Older patients developed less RNFL loss: at 6-months, an older ON patient manifested 18 μm (p=0.015) less RNFL thinning than a patient 10 years younger.

Conclusions:
SD-OCT captured progressive changes in RNFLT and MV for up to a year after ON. The impact of gender, age, and other factors needs to be considered in future trials using OCT as an outcome measure in ON and MS patients.

References:


Keywords: Optic neuritis, Multiple Sclerosis, Retinal Nerve Fiber Layer, Optical Coherence Tomography, Clinical Models

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TrkB Neurotrophin Receptor Activation with Pharmacophore as Possible Treatment for Anterior Ischemic optic Neuropathy

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1Stanford Department of Ophthalmology, Stanford, CA, USA, 2Stanford Department of Neurology, Stanford, CA, USA, 3Stanford Department of Neurobiology, Stanford, CA, USA

Introduction:
Anterior ischemic optic neuropathy (AION) is the most common acute optic neuropathy in older adults, and there is currently no effective treatment. Retrogradely transported neurotrophins like BDNF (brain-derived neurotrophic factor) and its high affinity receptor TrkB are particularly important in the survival of retinal ganglion cells (RGCs) following injury, leading to the hypothesis that restoration of neurotrophic support may be an effective therapeutic approach. In this study, we tested the effects of LM22A-4, a small molecule pharmacophore that specifically activates the TrkB receptor with nanomolar affinity, on RGC survival and as treatment of experimental AION.

Methods:
We cultured rodent neonatal RGCs using immunopanning. On culture day-2, we calculated RGC survival and assessed TrkB receptor activation by morphometric analysis of MAP kinase translocation. To test in vivo effects, we performed one intravitreal and 3-week daily systemic treatment immediately following murine AION and measured retinal thickness with spectral-domain optical coherence tomography (SD-OCT).

Results:
In vitro, LM22A-4 treatment significantly increased RGC survival (drug: 27.0 ± 1.5%; negative control: 11.0 ± 3.9%; P <0.0001), similar to the effect of BDNF (27.1 ± 1.2%). This improved survival correlated with significant nuclear and cytoplasmic translocation of MAP kinase (P <0.0001), a molecule downstream of TrkB receptor. In vivo treatment for 3-weeks after AION lead to significant preservation of retinal thickness in SD-OCT circular analysis (12º) of the ganglion cell complex (N = 15 eyes/condition, P = 0.01) and posterior pole analysis of the optic disc (N = 8-10 eyes/condition, P = 0.02). This in vivo improvement was partial, similar to that of BDNF or antibodies that activate TrkB receptor in other experimental optic neuropathies.

Conclusions:
Pharmacophore LM22A-4 promoted TrkB receptor activation and RGC survival in vitro similar to endogenous ligand BDNF. Treatment for 3-weeks in vivo following murine AION led to partial rescue of retinal thinning on SD-OCT, suggesting LM22A-4 may be effective treatment for AION.

References:

Keywords: Anterior Ischemic Optic Neuropathy, Neurotrophin, TrkB, Retinal Ganglion Cells, Treatment

Financial Disclosures: Dr. Frank Longo has earned consulting fees and has equity interest in the company PharmatrophiX, which produces LM22A-4. No other authors had disclosures.
Monday, February 11, 6:15 - 6:30 p.m.

Progranulin Deficiency Causes TDP43 Mislocalization and Neuron Death in the Retina

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Introduction:
Neurodegeneration and cytoplasmic mislocalization of TDP43 are pathologic hallmarks of sporadic frontotemporal lobar dementia—TDP-43 subtype (FTLD-TDP) and familial FTLD caused by GRN mutations. However, the relationship between progranulin (PGRN)-deficiency, TDP43 mislocalization, and neuronal death remains unclear. Though brains from PGRN-deficient mice display some pathologic features of FTLD, neither a robust neurodegenerative phenotype nor TDP43 redistribution occurs. As such, fundamental aspects of FTLD pathogenesis have been difficult to model in these mice. Because retinal abnormalities are early feature of other neurodegenerative diseases, suggesting that retinal neurons are an especially vulnerable cell population in the CNS, we investigated whether retinal pathology occurred in a mouse model of GRN-deficient FTLD.

Methods:
We used optical coherence tomography (OCT) to determine if retinal nerve fiber layer (RNFL) thinning occurred in FTLD subjects, including those with GRN mutations, compared to non-demented controls. In addition, we investigated if Grn-deficient mice exhibited FTLD pathology in the retina using standard immunostaining techniques.

Results:
Retinal imaging of FTLD subjects via OCT revealed significant RNFL thinning compared to non-demented controls. FTLD subjects with known GRN mutations also exhibited significant RNFL thinning. In Grn-KO mice we observed progressive RNFL thinning and death of retinal ganglion cells (RGCs). Notably, we observed nuclear depletion of TDP-43 in Grn-KO RGCs prior RGC death, a characteristic pathologic finding in human GRN-deficient FTLD. Unexpectedly, we did not observe TDP-43 inclusions in Grn-KO mice.

Conclusions:
We observed a new retinal phenotype in FTLD patients that is recapitulated in a mouse model of this disease. Our findings of RGC loss preceded by nuclear depletion of TDP-43, in the absence of inclusions, suggests that—in the retina—cell death may occur through a loss of normal function of nuclear TDP-43. In addition, our findings indicate that OCT imaging may be useful as a diagnostic tool in FTLD patients.

Keywords: OCT, Retinal Ganglion Cells, Dementia, TDP-43, Progranulin

Financial Disclosures: The authors had no disclosures.
Intravitreal Injection Of Bevacizumab May Be Neuroprotective In A Mouse Model Of Optic Nerve Crush

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Introduction:
Disk edema may exacerbate axonal damage in acute optic neuropathy. Bevacizumab (Avastin®) inhibits the signaling of Vascular Endothelial Growth Factor (VEGF), thereby potentially reducing the vasogenic edema of the disk. The aim of this study was to evaluate the effect of an intravitreal injection of bevacizumab on optic nerve edema and RGC loss in a mouse model of optic nerve crush (ONC).

Methods:
ONC was induced in the right eye of 50 C57BL6 wild type mice. Bevacizumab was injected intravitreally to 25 of them immediately afterwards. A control group (n=25) had a single intravitreal Bevacizumab injection without crush. The left eye of each mouse was used as a healthy control. Evaluation included: quantitative real-time PCR for gene expression of Heme-oxegenase-1 (Ho-1), Superoxide-Dismutase (SOD) and VEGF on days 1,3. Histological and immunohistochemistry analysis of optic nerves and retina on days 1,3 and 21. Fluorescein angiography (FA) was taken on days 0, 1 and 3 following ONC induction with and without intravitreal injection of bevacizumab.

Results:
FA following ONC showed disk leakage and vascular dilatation. When ONC was followed by intravitreal Bevacizumab injection there was no disk leakage nor vascular dilatation. Following intravitreal Bevacizumab injection or ONC, gene expression of HO-1 and SOD increased. HO-1 and SOD levels further increased when ONC was followed by Bevacizumab injection. VEGF expression decreased following intravitreal Bevacizumab injection, remained at baseline after ONC, and was slightly elevated after ONC and Bevacizumab injection. This was confirmed by immunohistochemistry. 52% of the RGC lossed 21 days following ONC. Bevacizumab injection reduced this loss to 14%, a level similar to Bevacizumab injection alone (15%).

Conclusions:
Bevacizumab has a protective effect following ONC damage demonstrated by reduced optic nerve head edema, reduced RGC loss, and reduced upregulation of antioxidative and ischemic genes.

Keywords: Bevacizumab, Optic Neuropathy, Neuroprotective, Mouse Model

Financial Disclosures: The authors had no disclosures.
Monday, February 11, 6:45 - 7:00 p.m.

Subclinical Optic and Retinal Atrophy in Eyes with Papilledema detected by OCT.

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Introduction:
As the appearance of papilledema seems to improve, it is difficult to distinguish whether this represents resolution of swelling or merely superimposed optic atrophy requiring further treatment. We hypothesize that automated Spectral Domain OCT (SDOCT) segmentation can detect subclinical optic atrophy in chronically swollen optic nerves. Idiopathic intracranial hypertension (IIH) serves as a model to study optic nerve damage caused by papilledema since confounders such as compression or inflammation are absent.

Methods:
Patients with papilledema due to IIH were identified by chart review. Eyes with active papilledema (Frisen grade>2) were excluded. Remaining eyes were subdivided: atrophic papilledema (optic nerve pallor or vision/visual field changes) and mild papilledema (no pallor, normal vision). Scans were reviewed for retinal abnormalities. Automated SDOCT segmentation of nerve fiber layer (NFL), ganglion cell/inner plexiform (GCL/IPL) layer, and remaining outer retina were compared to age matched controls. One eye from each patient was used for analysis.

Results:
Twenty eyes had mild papilledema; eight eyes had optic atrophy. Mild papilledema eyes had normal retinal architecture; all atrophy eyes had structural retinal abnormalities such as inner nuclear layer cysts, photoreceptor loss, or epiretinal membrane. Compared to controls, mild papilledema eyes had similar average RNFL, increased inferior RNFL(1690μm vs. 129μm, p=0.02/bonferroni-p=0.05), decreased inner macular GCL/IPL thickness (331μm vs. 343μm, p=0.01/bonferroni-p=0.03), and decreased outer retinal layers thickness in the central macula, as well as the inner and outer macular rings (212μm vs. 221μm, p=0.01; 211μm vs. 220μm, p=0.01/bonferroni-p=0.02; 185μm vs. 192μm, p=0.02/bonferroni-p=0.04).

Conclusions:
OCT can detect inner and outer retinal structural changes associated with papilledema. Eyes with mild papilledema and no clinically detected optic atrophy have thinning of the NFL, GCL/IPL and outer retina. This suggests that papilledema causes both retinal and optic nerve atrophy. Further longitudinal studies with larger numbers are warranted.

Keywords: Papilledema, Optical Coherence Tomography, Macular Segmentation

Financial Disclosures: The authors had no disclosures.