Platform Session I

Arizona Salons 1-6

Monday, March 8, 2010

5:00 – 7:00 p.m.

Moderators: Nicholas Volpe, MD and Janine Johnston, MD, FRCP(C)

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5:00 p.m. - 5:15 p.m.

Double-Blind Cross-Over Trial of Gabapentin and Memantine for Treatment of Acquired Nystagmus

Matthew Thurtell[1], Anand Joshi[2], Alice Leone[2], Robert Tomsak[2], Gregory Kosmorsky[3], John Stahl[2], John Leigh[2]

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Introduction:
Acquired nystagmus commonly produces disabling visual symptoms, such as blurred vision and oscillopsia. Prior prospective studies have shown that gabapentin is effective for treating acquired nystagmus, especially acquired pendular nystagmus (APN). Recent studies have demonstrated that memantine is also effective for treating APN. We therefore aimed to prospectively compare gabapentin and memantine as treatments for a variety of types of acquired nystagmus, including APN and oculopalatal tremor.

Methods:
Using a double-blind cross-over design, we compared memantine (40mg/day) with gabapentin (1200mg/day) as treatment for acquired nystagmus in 10 patients (ages 28-61; 7 female; 3 from MS, 6 following stroke, and 1 following head injury). The nystagmus was pendular in 6 patients (4 patients had oculopalatal tremor, and 2 had APN due to MS), and upbeat, hemi-seesaw, torsional, or diagonal in the other 4 patients. We measured visual acuity and recorded eye movements using the magnetic search coil technique before and after 2 weeks of treatment on each drug, with a 2-3 week wash-out period between them. We calculated the median speed of the nystagmus slow-phase from desaccaded data.

Results:
Visual acuity improved with both drugs; the change was significant for memantine (p=0.00, paired t-test), but not for gabapentin (p=0.07). Both drugs reduced the median speed of the nystagmus (p=0.001), decreasing it by 32.8% for gabapentin and 27.8% for memantine. The improvements were idiosyncratic and unrelated to the etiology or waveform of the nystagmus. We did not see a priming or carry-over effect with either drug (p>0.05). Both drugs were well tolerated, with the most common side-effects being unsteadiness with gabapentin and lethargy with memantine.

Conclusion:
Our study confirms that both gabapentin and memantine can be effective for treatment of acquired nystagmus, although the response is idiosyncratic. The risk of exacerbating neurologic symptoms mitigates against use of memantine for treatment of acquired nystagmus in MS.

References:
1. Averbuch-Heller L, Tusa RJ, Fuhry L, Rottach KG, Ganser GL, et al. A double-blind controlled study of gabapentin and baclofen as treatment for acquired nystagmus. Ann Neurol 1997; 41: 818-825.
2. Bandini F, Castello E, Mazzella L, Mancardi GL, Solaro C. Gabapentin but not vigabatrin is effective in the treatment of acquired nystagmus in multiple sclerosis: how valid is the GABAergic hypothesis? J Neurol Neurosurg Psychiatry 2001; 71: 107-110.
3. Shery T, Proudlock FA, Sarvananthan N, McLean RJ, Gottlob I. The effects of gabapentin and memantine in acquired and congenital nystagmus: a retrospective study. Br J Ophthalmol 2006; 90: 839-843.
4. Starck M, Albrecht H, Pollmann W, Dieterich M, Straube A. Acquired pendular nystagmus in multiple sclerosis: an examiner-blink cross-over treatment study of memantine and gabapentin. J Neurol 2009; doi:10.1007/s00415-009-5309-x.
5. Villoslada P, Arrondo G, Sepulcre J, Alegre M, Artieda J. Memantine induces reversible neurologic impairment in patients with MS. Neurology 2009; 72: 1630-1633.

Key Words: Nystagmus, Oscillopsia, Multiple Sclerosis, Oculopalatal Tremor

Financial Disclosure: NONE

5:15 p.m. - 5:30 p.m.

Sensitivity and Specificity of a New "Upright-Supine Test" to Differentiate Skew Deviation from Other Causes of Vertical Strabismus

Agnes Wong, Linda Colpa

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Introduction:
In a previous study, we demonstrated that the vertical strabismus in patients with skew deviation decreased substantially when they changed from an upright to supine position, whereas in patients with trochlear nerve palsy, the vertical strabismus changed minimally between these two positions. The purpose of this study is to determine the sensitivity and specificity of this new "upright-supine test" to differentiate skew deviation from other causes of vertical strabismus in a large number of patients.

Methods:
Seventeen patients with skew deviation, 40 with trochlear nerve palsy, and 25 with other causes of vertical strabismus (e.g., dysthyroidism, orbital trauma, Brown syndrome, myasthenia gravis, childhood strabismus, peripheral oculomotor nerve palsy) were recruited. Vertical strabismus was measured by the prism and alternate cover test using a near target at 1/3 meter in both the upright and supine position. A vertical strabismus that decreased by ≥50% from the upright to supine position constituted a positive test.

Results:
Thirteen patients with skew deviation had a positive "upright-supine test", giving the test a sensitivity of 76%. No patients with trochlear nerve palsy or other causes of vertical strabismus had a positive test, giving the test a specificity of 100%. All four patients with skew deviation who had a negative test exhibited other neurologic signs and had a lesion in the midbrain on MRI, which may have caused a vertical strabismus from a combination of skew deviation, trochlear and/or oculomotor nerve palsy.

Conclusion:
The upright-supine test is highly specific for the detection of skew deviation. Because skew deviation can mimic a trochlear nerve palsy during the "three-step" test, the upright-supine test should be added as a fourth step—if it is positive, neuroimaging should be ordered to rule out a skew deviation even if the three-step test indicates a trochlear nerve palsy.

References: NONE

Key Words: Skew Deviation, Trochlear Nerve Palsy, Head Position, Fourth Nerve Palsy

Financial Disclosure: NONE

5:30 p.m. - 5:45 p.m.

Static Ocular Counterroll in Patients with Skew Deviation

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Introduction:
Static ocular counterroll (OCR) generates compensatory torsional eye movements during static head tilt and it is mediated by the utricles in the inner ear. Skew deviation is a vertical strabismus thought to be caused by imbalance of the VOR pathway that originates from the utricles and projects to ocular motoneurons (i.e. the utriculo-ocular pathway). We hypothesized that if skew deviation is indeed caused by damage to utricular-ocular pathway, patients with skew deviation would show abnormal static OCR gain.

Methods:
Seven normal subjects and seven patients with skew deviation caused by brainstem or cerebellar lesions were recruited. With one eye occluded, subjects viewed a red laser spot against a grid pattern at 1 m. Ocular responses to static passive head roll-tilts of about 20 deg toward each shoulder was recorded using scleral search coils. Static OCR gain was calculated as the change in torsional eye position divided by change in head position during sustained head tilt.

Results:
OCR gains were decreased in both eyes and in both tilt directions. In the hypertropic eye, mean counterclockwise (during clockwise head tilt from subject's point of view) OCR gain was 46.1% lower in patients (0.099 in patients vs 0.184 in controls; p=0.024), whereas in the clockwise direction, it was 61.7% lower in patients (0.075 vs 0.196; p=0.0018). In the hypotropic eye, mean counterclockwise OCR gain was 49.8% lower in patients (0.092 vs 0.184; p=0.014), whereas in the clockwise direction, it was 61.1% lower in patients (0.077 vs. 0.196; p=0.00046).

Conclusion:
The decrease in static OCR gain in patients with skew deviation provides support that disruption of the utricular-ocular pathway is a mechanism for skew deviation.

References: None

Key Words: Abnormal Static Ocular Counterroll, Skew deviation, Utricular-ocular pathway, imbalance of VOR, Ocular motoneurons

Financial Disclosure: NONE

5:45 p.m. - 6:00 p.m.

Neurofibromatosis Type 1 Associated Optic Glioma Visual Outcomes Following Chemotherapy: A Multi-center Retrospective Analysis

Michael J. Fisher[1], Laura Balcer[2], Robert Listernick[3], David Gutmann[4], Roger Packer[5], Rosalie Ferner[6], Robert Hoffman[7], Uri Tabori[8], Eric Bouffet[8], Darren Hargrave[9], Joel Charrow[3], Janice Lasky Zeid[3], Anne Albers[4], Annie Kuo[7], Michael Loguidice[2], Angie Miller[1], Grant Liu[1]

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Introduction:
Optic gliomas (OPGs) arise in 15-20% of children with neurofibromatosis type 1 (NF1); nearly half become symptomatic. Much of the literature on treatment with chemotherapy has focused on radiographic outcomes. In contrast, despite nearly two decades of experience in treating NF1-associated OPG with chemotherapy, there is a paucity of information regarding the ophthalmologic outcome of these children.

Methods:
A retrospective study of six large NF1/Neuro-Oncology centers was undertaken to evaluate visual outcomes following chemotherapy for NF1-associated OPG, to identify risks for visual loss, and to define the indications for treatment. Subjects included children undergoing initial treatment for OPGs with chemotherapy between January 1997 and December 2007.

Results:
Of the 79 subjects, approximately 1/3 had tumors of the anterior visual pathway (nerves and/or chiasm). Visual acuity (VA) decline and tumor progression were the primary reasons to initiate treatment; however, for most subjects, more than one factor spurred treatment (mean=2.19, range 1-7), including tumor size/extent, tumor location, progressive proptosis, and inability to obtain reliable VA.

Sixty-five subjects were evaluable for VA outcomes. At completion of chemotherapy, VA improved (34%), remained stable (43%), or declined (23%). Notably, VA improved in 42% of anterior-OPGs, but only 23% of tumors located in the optic tracts/radiations. In contrast, VA worsened in 33% of tract/radiation tumors and 17% of anterior-OPGs. Gender, NF1 type (familial vs. sporadic), and age did not appear to be risk factors for visual acuity outcome.

Conclusion:
Although most patients with OPG have improvement or stabilization of vision after treatment with chemotherapy, VA worsens in 1/4 of subjects despite treatment. In particular, tumor location in the optic tracts/radiations appears to be a risk factor for poor visual outcome.

References: NONE

Key Words: optic glioma, neurofibromatosis type 1, visual acuity, outcomes, chemotherapy

Financial Disclosure: NONE

6:00 p.m. - 6:15 p.m.

Low-Contrast Letter Acuity Detects Visual Function Improvement in Phase 3 Relapsing MS Trials of Natalizumab

Laura Balcer[1], Steven Galetta[1], Chris Polman[2], Richard Rudick[3], Frederick Munschauer[4], Peter Calabresi[5], Eric Eggenberger[6], Annie Zhang[7], Richard Kim[7]

[1]University of Pennsylvania School of Medicine, Philadelphia, PA, United States, [2]VU Medical Center, Amsterdam, Netherlands, [3]Cleveland Clinic Foundation, Cleveland, OH, United States, [4]Buffalo General Hospital, Buffalo, NY, United States, [5]Johns Hopkins University School of Medicine, Baltimore, MD, United States, [6]Michigan State Univerisity, East Lansing, MI, United States, [7]Biogen Idec, Cambridge, MA, United States

Introduction:
In the AFFIRM trial, natalizumab reduced sustained visual loss by low-contrast letter acuity (LCA), but not high-contrast visual acuity (HCA). Natalizumab was associated with improvements in disability and quality of life; we determined whether similar improvements could be demonstrated for vision. We examined the probability of visual improvement and its association with treatment status in the pivotal phase 3 trial of natalizumab.

Methods:
Vision testing was performed binocularly for HCA and LCA. Cumulative probabilities of visual improvement, sustained over 12 weeks, were determined for increases in score by 1 line (5 letters) and 2 lines (10 letters). Improvement by 7 letters was also examined as a threshold since this represents the upper limit of test-retest variability based on reliability studies of LCA.

Results:
The probability of visual improvement, defined as ≥7-letter score increase from baseline, sustained for 12 weeks, was greater for natalizumab (n=627) vs. placebo (n=314). This was observed for LCA at 2.5% contrast (21% vs. 13% with improvement, hazard ratio=1.57, p=0.012) and 1.25% contrast (32% vs. 24%, hazard ratio=1.39, p=0.014, Cox proportional hazards models). HCA showed a much lower probability of improvement (~6%) that did not differ between treatment groups. Natalizumab was associated with greater proportions of patients showing improvement from baseline for at least 8/10 study visits by LCA (2.5%: 23% vs. 15% for placebo, p=0.013; 1.25%: 28% vs. 23%, p=0.043). There was a greater degree of improvement across all visits for natalizumab by 2.5% contrast (p=0.003), with a trend for 1.25% (p=0.055). Probabilities of improvement at threshold levels below (5 letters) and above (10 letters) test-retest variability did not show treatment differences.

Conclusion:
Natalizumab is associated with sustained visual improvement by some measures of visual function; this improvement is particularly well-captured by the 2.5% contrast chart. HCA was less sensitive and failed to capture clinically-relevant improvements in visual function.

References:
1. Balcer LJ, Galetta SL, Calabresi PA, et al. Natalizumab reduces visual loss in patients with relapsing multiple sclerosis. Neurology 68:1299-1304, 2007.
2. Rudick RA, Panzara MA. Natalizumab for the treatment of relapsing multiple sclerosis. Biologics: targets & therapy 2:1-11, 2008.
3. Balcer LJ, Baier ML, Pelak VS, et al. New low-contrast vision charts: reliability and test characteristics in patients with multiple sclerosis. Mult Scler 6:163-171, 2000.

Key Words: multiple sclerosis (MS), visual function, low-contrast letter acuity, natalizumab,

Financial Disclosure: Dr. Balcer has received honoraria for consulting from Biogen Idec and Bayer for development of visual outcome measures for MS trials. Dr. Galetta has received speaking honorarium from BiogenIdec and Teva Pharmacueticals. Dr. Polman received personal compensation from Biogen Idec, Bayer Schering, TEVA, Merck Serono, Novartis, Glaxo SK, Actelion, UCB, Roche for consulting services. Drs. Zhang and Kim are employed by Biogen Idec.

6:15 p.m. - 6:30 p.m.

Neuronal Protection of the Retinal Ganglion Cell

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Introduction:
Neuronal injury and cell loss are often changes noted on neuro-ophthalmic exam. No therapies exist to date to protect or revive these damaged structures. Evidence is accumulating that the heat shock response (hsr) is neuroprotective against a wide variety of insults both in vitro and in vivo. Some of these agents may be neuro-regenerative as well. The goal of our current studies was to determine if stimulating the heat shock response has a neuroprotective effect on human retinal ganglion cells (RGCs).

Methods:
A well-established retinal ganglion cell line (RGC-5) was cultured by standard previously described methods. Doxorubicin, a known oxidative apoptotic agent, was added to cells at various concentrations. Cells were harvested and viability was determined after trypan blue staining using a Cellometer (Nexcelcom Biosciences). An experimentally convenient dose was established (5 µg/ml) and used in all subsequent studies. RGC-5 cells were then pre-incubated with various concentration of celastrol (CSA) or geldanamycin (GA), known chemical inducers of the hsr. Thereafter, cells were exposed to doxorubicin and at various times post-insult the number of viable cells was quantitated.

Results:
We first studied the dose and time-dependent nature of RGC cell death in the presence of doxorubicin. At a doxorubicin concentration of 5 µg/ml there was 60% cell death after 24 hrs incubation. In the presence of either CSA or GA there was a statistically significant reduction in cell death to about 20%. Analysis of doxorubicin exposed cells treated with the placebo (DMSO) showed profound morphological changes associated with apoptosis. Additionally, IF revealed that either CSA or GA-treated cells showed minimal apoptotic features.

Conclusion:
For the first time, we demonstrate that stimulating the heat shock response in RGC's provides neuroprotection against doxirubicin-induced apoptosis. There are a variety of chemicals which stimulate the heat shock response in different ways. These compounds may clinically provide neuroprotection to the retinal ganglion cells, allowing us to mitigate RGC loss in such diseases as non-arteritic anterior ischemic optic neuropathy, glaucoma and mitochondrial diseases. One of them is an FDA-approved medication. We will discuss other preliminary clinical experience with that drug.

References:
1. Quigley HA, Nickells RW, Kerrigan LA, et al. Retinal ganglion cell death in experimental glaucoma and after acotomy occurs by apoptosis. Invest Opthalmol Vis Sci. 36:774-786; 1995.
2. Wang S, Konorev EA, Kotamraju S, et al. Doxorubicin induces apoptosis in normal and tumor cells via distinctly different mechanisms. J Biol Chem. 2004; 279:25535-25543.
3. Chuang DM. The antiapoptotic actions of mood stabilizers: molecular mechanisms and therapeutic potentials. Ann N Y Acad Sci. 2005 Aug; 1053:195-204.
4. Marinova Z, Ren M, Wendland JR, Leng Y, Liang MH, Yasuda S, Leeds P, Chuang DM, Valproic acid induces functional heat-shock protein 70 via Class I histone deacetylase inhibition in cortical neurons: a potential role of Sp1 acetylation. J Neurochem.; 111(4):976-87. 2009 Nov Epub 2009 Sep 18.

Financial Disclosure: NONE

6:30 p.m. - 6:45 p.m.

The Birmingham Weight loss in Idiopathic Intracranial Hypertension and Intracranial Pressure Study

Michael Burdon[1], Alexandra Sinclair[1], Peter Nightingale[1], Alexandra Ball[1], Peter Good[2], Tim Matthews[2], Andrew Jacks[2], Mark Lawden[3], Carl Clarke[1], Elizabeth Walker[1], Jeremy Tomlinson[1], Paul Stewart[1], Saaeha Rauz[1]

[1]University of Birmingham, Birmingham, United Kingdom, [2]Birmingham Neuro-ophthalmology Unit, University Hospitals Birmingham NHS Foundation Trust, Birmingham, United Kingdom, [3]Department of Neurology, Leicester General Hospital, Leicester, United Kingdom

Introduction:
Idiopathic intracranial hypertension (IIH) is characterized by elevated intracranial pressure (ICP) leading to visual loss and disabling headaches affecting predominantly obese females. Weight loss is a frequently advocated treatment, although efficacy has to date, not been convincingly demonstrated. We describe the results from the first prospective weight reduction study in adults with chronic active IIH.

Methods:
25 female subjects with papilloedema (weight 101.3±16.5kg, ICP 39.5±4.6cmH_2O, Headache Impact Test-6 (HIT) score 59.2±9.0, disease duration 39.0±49.2 months (mean± SD)) were studied. A three month period of no new intervention (stage 1) was followed by a strict low calorie diet (425 Kcal/day) for three months (stage2). Assessments of ICP (measured by lumbar puncture), papilloedema, visual function and headache were conducted at baseline, three and six months.

Results:
All parameters remained stable over stage 1. During stage 2, there were significant reductions in: weight (14.2±7.8kg($p<0.001$)), ICP (8.3±4.1 cmH_2O($p<0.001$)), HIT (7.7±10.2($p=0.004$)) and papilloedema as measured by ultrasonography of the optic nerve (optic disc elevation ($p=0.002$) nerve sheath diameter ($p=0.004$)) and ocular coherence tomography of the peripapillary retina ($p=0.001$), whilst the Humphrey visual field mean deviation remained stable and the LogMAR visual acuity improved by one line in 30.4. Symptoms including tinnitus, diplopia and obscurations resolved ($p=0.004$, 0.008 and 0.025 respectively). Re-evaluation at three months post-diet revealed no significant change in weight (0.21±6.8 kg) and all outcome measures were maintained.

Conclusion:
This is the first study to conclusively demonstrate that weight loss is effective at reducing not only headaches and papilloedema, but also ICP in IIH.

References: NONE

Key Words: Idiopathic intracranial hypertension, Weight loss, Intracranial Pressure, ultrasonography, Optical coherance tomography

Financial Disclosure: NONE

6:45 p.m. - 7:00 p.m.

Retinal Nerve Fiber Layer Thickness Measured by Optical Coherence Tomography is Decreased in Children with Vision Loss from Optic Pathway Gliomas

Grant Liu, Robert Avery, Laura Balcer, Michael Fisher, Maureen Maguire, Jean Belasco, Graham Quinn, Angie Miller, Peter Phillips

Children's Hospital of Philadelphia, Philadelphia, PA, United States

Introduction:
Visual acuity (VA) is commonly used to screen and monitor visual function in children with optic pathway gliomas (OPG). However, obtaining reliable VA measures can be difficult in some children with OPG. Thus, an objective quantitative biomarker for visual integrity is needed in such instances. Optical coherence tomography (OCT) has been used to measure retinal nerve fiber layer (RNFL) thickness in adults with tumors compressing the optic chiasm. Therefore, we investigated whether RNFL thickness could serve as a biomarker for visual loss in children with OPG.

Methods:
Patients between 6 and 21 years old with and without vision loss from their OPG underwent best corrected VA testing of each eye with the "Electronic Visual Acuity" tester [Moke et al., 2001] using surrounded HOTV letters and Sloan 2.5% low contrast acuity (SLCA). Average RNFL thickness was measured with the time-domain OCT using the fast RNFL thickness protocol. Vision loss was defined as a VA > 0.1 log MAR or visual field loss.

Results:
49 subjects provided 87 study eyes (50 with normal vision and 37 with vision loss). Median VA was 0.0 versus 0.5 log MAR in the normal versus abnormal vision groups. The median number of correctly identified letters for the 2.5% SLCA was lower in the abnormal (13) versus normal (35) vision group ($z = 6.5$, $p < 0.0001$). RNFL thickness was lower in the abnormal (64 ± 23 microns) versus normal (104 ± 25 microns) vision groups ($t = 7.5$, $p < 0.0001$). RNFL thickness was significantly correlated with VA ($r = -.52$, $p = 0.0001$) and 2.5% SLCA ($r = 0.60$, $p < 0.0001$).

Conclusion:
RNFL thinning in children with OPG correlates well with high-contrast VA and low-contrast letter acuity testing. RNFL thickness can be used as a biomarker of visual pathway integrity in children with OPG.

References:
1. Moke et al., Computerized method of visual acuity testing: Adaptation of the amblyopia treatment study visual acuity testing protocol.
2. American Journal of Ophthalmology, 132, 903-09, 2001.

Key Words: Optic pathway glioma, OCT, retinal nerve fiber layer, vision loss

Financial Disclosure: NONE