The relationship between the levonorgestrel-releasing intrauterine system and idiopathic intracranial hypertension


Purpose: Unconfirmed reports have linked the levonorgestrel-releasing intrauterine system (LNG-IUS), a long-acting contraceptive, to idiopathic intracranial hypertension (IIH). In this pilot case-control study, we compared LNG-IUS exposure between a cohort of patients with IIH and an analogous cohort of patients without IIH.

Methods: A retrospective series of 473 patients with ICD-9 codes for pseudotumor cerebri (PTC) was screened for female gender, age at onset of 18-55, diagnosis from 2008-2013, and non-idiopathic etiologies. Of the eligible participants, 59 completed telephone birth control histories of the 3 month timeframe preceding IIH onset. Records were then queried for CPT codes for LNG-IUS insertion in 220,904 women without ICD-9 codes for PTC who were aged 18-55 and had at least one clinical encounter from 2008-2013. Descriptive statistics and significance tests were performed, and odds ratios were calculated.

Results: Exposure to an LNG-IUS was significantly associated with the development of IIH (OR 7.7, 95% CI 3.2-16.4, p<0.001); the prevalence of IIH was 0.18% in the LNG-IUS population (8/4408, 95% CI 0.07-0.35) versus 0.02% in the non-LNG-IUS population (51/216555, 95% CI 0.01-0.03). Of those IIH patients not on an LNG-IUS, 9 (15%) were on another contraceptive and 42 (71%) were not on any contraceptives. All LNG-IUS users who developed IIH manifested symptoms while the device was still in situ. There were no significant differences between LNG-IUS users and non-users in terms of age, body mass index, recent weight gain, or presenting signs and symptoms.

Conclusions: Our findings suggest that LNG-IUS exposure does not alter the clinical features of IIH; however, it is disproportionately more common among IIH patients than non-IIH patients. Therefore, although a causative role for LNG-IUS has not yet been established, we recommend augmenting the routine evaluation of IIH with a birth control history. IIH patients who are considering options for birth control should be counseled about the possible connection between LNG-IUS and IIH. While the preliminary evidence does not warrant the removal of an LNG-IUS in a typical IIH patient, atypical IIH patients (i.e., non-obese, having no other risk factors) with an LNG-IUS may wish to switch to an alternative contraceptive.

Commercial Relationships: Ruju Rai, None; Brian Kirk, None; Jessica Sanders, None; Reuben Valenzuela, None; Subhashree Sundar, None; Judith Warner, None; Kathleen B. Digre, None; Balamurali Ambati, None; Alison V. Crum, None; Bradley J. Katz, None

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and FPG were not associated (p=0.10, mann-whitney rank sum). SAP-MD was associated with GCCV (r=0.72, p=0.019, LR). Addition of FPG did not improve the LR model for SAP-MD. Log PhNR amplitude was also associated with GCCV (r=0.77, p=0.009, LR). Addition of FPG improved the LR model for PhNR (r=0.94, p<0.0001, p(GCCV)<0.0001, p(FPG)=0.003, LR).

**Conclusions:** Though visual and ganglion cell functional markers are modestly correlated, we find their individual correlations with structural markers to differ. Both SAP-MD and PhNR are related to ganglion cell atrophy, but only PhNR is also associated with degree of acute optic nerve pathology. The observation that high-grade papilledema is associated with PhNR decrease but not SAP-MD severity supports literature implicating PhNR association with pre-perimetric optic nerve injury. Further studies are needed to determine the clinical utility of PhNR as a marker for diagnosis and monitoring of IIH.

**Visual function (top) and Photopic negative response (bottom) as a function of ganglion cell complex volume (line) and papilledema grade (markers) in IIH subjects**

**Commercial Relationships:** Heather Moss, None; J Jason McAnany, None; Jason C. Park, None

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**Program Number:** 2231 **Poster Board Number:** B0084

**Presentation Time:** 3:45 PM–5:30 PM

**Correlation of opening pressure and Frisén grade of papilledema in pediatric patients with intracranial hypertension**

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**Purpose:** While clinicians are diagnosing idiopathic and secondary intracranial hypertension in pediatric patients with increasing frequency, a paucity of research regarding the diagnosis and clinical features of these conditions exists. We performed a retrospective chart review of pediatric patients with intracranial hypertension in order to examine the relationship between lumbar puncture opening pressure (LPOP) and the severity of papilledema grade utilizing the Modified Frisén Scale (MFS).

**Methods:** 130 patients presenting between 2007 and 2013 with lumbar puncture-confirmed intracranial hypertension were included in the study. Demographic data and exam findings from initial exam with an ophthalmologist were collected. The worse papilledema grade between the two eyes on initial exam was compared to LPOP using Spearman’s Rank Correlation Coefficient, “r.” A second reader rated the subjects’ fundus photos and the inter-rater reliability was calculated using Cohen’s chance-corrected kappa statistic, “k.”

**Results:** Of the 130 included patients, 78 were female and 52 were male. The mean age of patients evaluated was 12.3 years old (range 3-18). 39 subjects were diagnosed with secondary intracranial hypertension. Seventy four patients had their lumbar puncture performed on the same day as their eye exam. A statistically significant moderately positive correlation was found between LPOP and Frisén grade of papilledema (r=0.426, p-value=0.000153). Even including those whose LP and eye exam were performed on different days, there was a weakly positive correlation between the LPOP and papilledema grade (r=0.255, p-value of 0.003371). In addition, 236 optic disc photos of 119 patients were reviewed. The linear weighted kappa value indicating inter-rater reliability indicated a good strength of agreement (k=0.669).

**Conclusions:** In pediatric patients with intracranial hypertension, the severity of papilledema correlates positively with lumbar puncture opening pressure. This result confirms the findings of a recent study in adult patients1 and may be helpful in guiding the clinical management of patients afflicted with intracranial hypertension.

**References**

**Commercial Relationships:** Laura L. Scott, None; Shawn Aylward, None; David Rogers, None; Rachel E. Reem, None

**Support:** Ohio Lions Eye Research Foundation
Changes in basement membrane opening displacement within 1 hour following intracranial pressure lowering in subjects with and without idiopathic intracranial hypertension

Gautam Vangipuram, Heather Moss. University of Illinois, Chicago, IL.

**Purpose:** Changes in basement membrane (BM) contour in the region of the optic nerve head are a promising marker for intracranial pressure (ICP) changes in idiopathic intracranial hypertension (IIH) based on studies showing change following surgical and medical treatment for elevated ICP. Rapid changes in BM configuration associated with ICP lowering have yet to be studied. This study tests the hypothesis that changes in BM opening (BMO) displacement, a surrogate for BM contour, occur rapidly following ICP lowering via lumbar puncture (LP).

**Methods:** Within 1 hour prior to and following LP in seven (27-60 yrs old, 11-24mL CSF drained) prospectively recruited subjects, 20° OCT B-scan images centered on the right optic nerve head along the nasal/temporal axis were acquired. The BM and inner limiting membrane (ILM) were automatically segmented and manually corrected. Optic nerve head maximum nasal, temporal and cup thicknesses were calculated as the distance between the BM and ILM. BMO displacement was calculated at the nasal and temporal margins of the BMO referred to a straight line between the outer nuclear layer-inner segment junction 3 mm nasally and temporally from the optic nerve head (fig.). Based on LP opening pressure (OP), subjects were grouped as IIH (n=3, OP 28-55cm H2O, all with papilledema) or non-IIH (n=4, OP 10-20cm H2O, none with papilledema).

**Results:** Across all subjects, BM displaced posteriorly following LP (p=0.018 nasal, 0.063 temporal, Wilcoxon signed ranks (WSR)). Optic nerve thicknesses and cup depth did not change following LP (p=0.15, 0.87, 0.18, WSR). IIH subjects had greater optic nerve thicknesses, shallower cup depth, and a more anterior BMO prior to LP than non-IIH subjects (p=0.034 for all, Mann Whitney Rank Sum). IIH and non-IIH subjects did not differ in the pre-post LP change in BM displacement, optic nerve thickness or cup depth. Groups did not differ by age or amount of CSF drained.

**Conclusions:** Changes in BMO displacement occur within 1 hour of ICP lowering via LP in subjects with and without IIH. Changes in optic nerve head contour do not occur within 1 hour of ICP lowering in subjects with or without IIH. These observations align with reports of BMO changes preceding optic nerve changes in treated IIH and support the candidacy of BMO displacement as a non-invasive rapid marker of ICP changes.

**Commercial Relationships:** Gautam Vangipuram, None; Heather Moss, None

**Support:** Unrestricted departmental grant from Research to Prevent Blindness, Illinois Society for the Prevention of Blindness, NIH K23 EY-024345, NIH P30 EY-001792

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Program Number: 2234 Poster Board Number: B0087
Presentation Time: 3:45 PM–5:30 PM
Pointwise Visual Field Change in the Idiopathic Intracranial Hypertension Treatment Trial

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Purpose: The Idiopathic Intracranial Hypertension Trial (IIHTT) showed acetazolamide provided a modest but significant improvement in global visual field function using mean deviation. Here, we aim to further analyze 1) the rate and 2) the magnitude of individual visual field test location change in the treatment groups from baseline to primary end point (six months).

Methods: We evaluated 121 of the enrolled IIH subjects who had visual field testing at baseline, six months and 3 of 4 interim visits. At entry the SITA Standard 24-2 mean deviation was between -2 dB and -7 dB in the worst eye (study eye). Subjects from multiple study sites were randomized in a placebo-controlled trial of acetazolamide with both treatment groups receiving a weight reduction program. We used pointwise linear regression to classify each of the 52 visual field test locations in the study eye as improving or not using the criterion of a positive slope. In a separate analysis, differences in magnitude in dB from baseline to final visit for the groups were computed and ANOVA was used to determine the significance of differences at each location.

Results: On average, subjects had 36 of 52 test locations with improving visual thresholds over six months in the study eye. While slopes of both groups improved, there were no significant differences in slopes between the treatment groups. Thresholds improved across the visual field with the magnitude of the change from baseline to final visit in dB greatest and statistically significant around the blind spot and the nasal area especially in the acetazolamide group. The figure shows the difference in dB between the groups (effect size of acetazolamide point by point).

Conclusions: While there were significant positive trends (slopes) in visual thresholds over time for most participants there were no significant differences between the groups. However, acetazolamide treatment resulted in significant improvement in visual field function with the magnitude of the changes greatest in the nasal and pericentral areas; the latter is likely due to reduction in blind spot size related to improvement in papilledema.

Fig. 1. Semi-automated landmark placement

Fig. 2. Left: Neural canal shape model variations; Right: Shape measure in ACZ/placebo group at baseline, 3 months and 6 months

Commercial Relationships: Jui-Kai Wang, None; Patrick A. Sibony, None; Randy H. Kardon, Acorda (C), Department of Veterans Affairs Research Foundation, Iowa City, IA (S), Fight for Sight Inc (S), Novartis (C); Mark J. Kupersmith, None; Mona K. Garvin, The University of Iowa (P)

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Clinical Trial: NCT01003639

Point by point effect size in dB of acetazolamide found by subtracting the average change from baseline of the placebo group from the acetazolamide group.

Commercial Relationships: Michael Wall, None; Gideon Zamba, None
Support: NORDIC 1U10EY017281-01A1

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Purpose: To demonstrate the effect of therapy on quantitative imaging of papilledema in the Idiopathic Intracranial Hypertension Treatment Trial (IIHTT). The IIHTT showed that acetazolamide (ACZ) was efficacious in improving mild visual field loss in patients with IIH. We showed that spectral domain optical coherence tomography (SD-OCT) combined with custom 3-segmentation analysis provides reliable continuous measurements of structural changes in the optic nerve head and retina due to papilledema (OCT Sub-Study Committee, IOVS in press).

Methods: Eighty-nine (43 ACZ, 46 placebo treated) IIHTT subjects were evaluated at study entry and at 3 and 6 months with standard automated perimetry, Frensl grading of photos, high and low contrast visual acuity, and OCT imaging using the Cirrus SD-OCT. OCT data were analyzed using custom 3-D segmentation algorithms to calculate retinal nerve fiber layer (RNFL), total retinal thickness (TRT), optic nerve volume (ONHV), and retinal ganglion cell layer (GCL) measurements. Results for ‘study eyes’ (with worse perimetric mean deviation, PMD, at baseline) were used for most analyses.

Results: At study entry, distributions of OCT measures were similar in both treatment groups. At 6 months, ACZ group eyes showed greater mean reductions in RNFL (175 μm vs. 89 μm, p=0.001), TRT (220 μm vs. 113 μm, p=0.001), and ONHV (4.9 mm³ vs. 2.1 mm³, p=0.001) than placebo group eyes. For both treatment groups, subjects with weight loss ≥ 6% had greater mean reductions in RNFL (156 μm vs. 103 μm, p=0.01), TRT (201 μm vs 127 μm, p=0.003), and ONHV (4.3 mm³ vs. 2.6 mm³, p=0.002) than those with less weight loss. GCL thinning was minor in the ACZ (3.6 μm) and placebo (2.1 μm) groups. Interocular correlations were ≥ 0.8 for all 3-D segmentation derived measurements. At 6 months, RNFL, TRT, and ONHV correlated with Frensl grade (r=0.48-0.59, p=0.0001). At 6 months, the 21 eyes with GCL thickness <5% percentile of controls had worse PMD (p=0.01) and both high (p=0.05) and low (p=0.01) contrast acuity than for eyes with GCL ≥ 5% percentile.

Conclusions: OCT measures of swelling due to papilledema in IIH are effectively improved with ACZ and weight loss. In contrast to the strong correlation at baseline (IOVS in press), 6 month RNFL, TRT, and ONHV show only moderate correlations with papilledema grade.

Commercial Relationships: Mark J. Kupersmith, None

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Clinical Trial: NCT01003639

Program Number: 2236 Poster Board Number: B0089

Presentation Time: 3:45 PM–5:30 PM

Ultramicroscopic study of the Optic Nerve Sheath in Patients with Severe Vision Loss from Idiopathic Intracranial Hypertension - Results

Marla Davis1, Joshua W. Evans1, Sachin Kedar2, Deepa Ghatel, Peter Timoney1, Richard Kielar3, Bruce Maley4, William O’Connor5

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Purpose: The objective of our study is to describe microscopic changes in the optic nerve sheath (ONS) of patients with severe and/or progressive vision loss from IIH.

Methods: ONS specimens were obtained at ONS fenestration in IIH (cases) and enucleation for painful blind eye (controls). Both procedures were performed by a single surgeon. After fixation and staining, specimens were examined by masked experts using light (LM), transmission electron (TEM) and polarization (PM) microscopy for specimen quality and tissue anatomy (cellularity and collagen structure).

Results: Of 12 specimens, 7 (6 cases, 1 control) met diagnostic and quality criteria. For cases: Mean age was 31.25y; mean disease duration 57 days; Mean CSF OP 40.25cm water. Papilledema grades were II (3 eyes); III (1 eye); IV (2 eyes). 5/6 patients showed severe visual field loss (MD> 15 dB); 3/6 had acuity worse than 20/40 and 2/6 had RAPD. All had normal CSF contents. Control ONS was obtained from an enucleated eye of a 18y with childhood ocular trauma. Collagen abnormalities on TEM: irregular arrangement (all cases), collagen disruption and increased extracellular fluid (5/6 cases) while control ONS showed regular, compact, normal collagen. PM showed marked decrease in green yellow birefringence (>20% in all cases with <5% in 4 cases) compared to control ONS (75% birefringence) which confirmed abnormal collagen content and arrangement in cases. All 6 cases showed increased cellularity on LM and/or TEM with active fibroblasts (3/6 cases) and chronic inflammatory cells (lymphocytes) in all 6 cases.

Conclusions: Disruption and disorganization of dural collagen in the ONS from IIH points to significant shear forces on distal ONS from raised ICP while increased cellularity indicates tissue repair. These mechanical and inflammatory components could contribute to visual loss in IIH. Early aggressive medical and/or surgical treatment may be beneficial in IIH.

Commercial Relationships: Marla Davis, None; Joshua W. Evans, None; Sachin Kedar, None; Deepa Ghatel, None; Peter Timoney, None; Richard Kielar, None; Bruce Maley, None; William O’Connor, None

Support: Research to Prevent Blindness

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Presentation Time: 3:45 PM–5:30 PM

Ultramicroscopic study of the Optic Nerve Sheath in Patients with Severe Vision Loss from Idiopathic Intracranial Hypertension- Methodology

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Purpose: Very little is known about the anatomy and pathology of the optic nerve sheath (ONS) in normal and diseased states. The objective of our study is to explore microscopic changes in the ONS in patients with severe and/or progressive vision loss from IIH.

Methods: ONS specimens were obtained from patients with IIH after ONS fenestration (cases) and painful blind eye after enucleation (controls). Both procedures were performed by a single surgeon. A 2 x 1 mm ONS window was obtained, divided into 2 parts, fixed and stained per following protocol. Light Microscopy (LM): All specimens were formalin fixed, stained using Hematoxylin-Eosin and examined at 10x and 40x magnification. Transmission electron microscopy (TEM): All specimens were immediately

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fixed (in Operating room) using 4% paraformaldehyde and 3.5% glutaraldehyde on ice; washed in Cacodylate buffer; postfixed using Osmium tetroxide/buffer mixture; dehydrated through graded concentrations of ethanol washes; and resin embedded. Ultrathin sections were obtained, stained and examined in Philips Tecnai Biotwin 12 TEM at 2900X magnification. Polarization microscopy (PM): All specimens were stained using Picrosiris red and examined under polarization microscope using previously published methods. (Junqueira et al., 1979) Masked experts in LM, TEM and PM performed evaluations for specimen quality (desiccation, trauma and staining) and tissue anatomy (cellularity and collagen arrangement).

**Results:** Of 13 subjects and 16 eyes enrolled, 7 specimens (6 cases and 1 control) met inclusion and quality control criteria for analysis. Tissue was not obtained in 4 eyes at surgery. 2 specimens were excluded due to alternative diagnosis (meningioma, panophthalmitis). 3 specimens were excluded due to tissue desiccation resulting from increased time interval from resection to tissue fixation.

**Conclusions:** Adequate quantity and quality ONS specimens were obtained in patients undergoing ONS fenestration and enucleation. Since ONS is susceptible to desiccation, tissue should be fixed immediately in the operating room.

**Commercial Relationships:** Joshua W. Evans, None; Marla Davis, None; Sachin Kedar, None; Deepa Ghate, None; Peter Timoney, None; Richard Kielar, None; Bruce Maley, None; William O’Connor, None

**Support:** Research to Prevent Blindness

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**Program Number:** 2238 **Poster Board Number:** B0091 **Presentation Time:** 3:45 PM–5:30 PM

**Multicolor imaging in the assessment and diagnosis of optic disc swelling**

**Andy Malen, Stephanie West, Gabriella De Salvo. Southampton General Hospital, Southampton, United Kingdom.**

**Purpose:** To examine the use of the recently developed Multicolor imaging (Heidelberg Spectralis) as an adjunct to traditional imaging modalities in the assessment of patients with suspected optic disc swelling, and to determine whether Multicolour (MC) can help in the differential diagnosis between true optic disc swelling and pseudopapilloedema.

**Methods:** Prospective consecutive study of 19 patients who presented to our clinic with suspected bilateral optic disc swelling. MC was performed on all patients in addition to fundoscopy, retinal nerve fiber layer optical coherence tomography (OCT) and fundus autofluorescence (FAF). MC combines three different wavelengths to enhance different retinal layers: 488nm (blue), 536nm (green) and 543nm (red). All images were analyzed by a medical retinal specialist.

**Results:** Of the 19 cases, 12 (63%) were female and 7 (37%) were male, with an average age of 19. Diagnosis of true papilloedema versus pseudopapilloedema was confirmed in all patients with a multidisciplinary approach. In fact 17 (89%) patients had raised intracranial pressure (ICP) confirmed by lumbar puncture opening pressure or brain imaging, and 2 (11%) had optic disc drusen. In those with true optic disc swelling secondary to raised ICP, MC illustrated a green shift correlating to the thickened retinal nerve fiber layer (RNFL) seen both clinically and on the optic disc OCT. The disc margins were indistinguishable at the green reflectance and a double ‘shadow’ was seen on the NIR reflectance. Unlike those with raised ICP, the patients with optic disc drusen did not present a green shift on the MC image and the disc margins were well delineated by a ring of hyperreflectance seen at the green reflectance; no thickening of the RNFL was detected.

**Conclusions:** Our results show that MC is a useful additional imaging modality in the diagnosis of true swollen optic discs and can provide additional information to help determine the underlying diagnosis in true and pseudopapilloedema.

**Commercial Relationships:** Andy Malen, None; Stephanie West, None; Gabriella De Salvo, None

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**Program Number:** 2239 **Poster Board Number:** B0092 **Presentation Time:** 3:45 PM–5:30 PM

**Papilledema Associated with Infantile Hypophosphatasia and Craniosynostosis**

**Constance E. West, Robert B. Hufnagel, Howard M. Saal.**

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**Purpose:** Hypophosphatasia (HPP) is a rare disease caused by reduced activity of alkaline phosphatase (ALP), and is secondary to mutations in ALPL, the gene encoding tissue-nonspecific ALP (TNSALP). There are at least six clinical forms and the spectrum of disease is wide, ranging from stillbirth to pathologic fractures in adulthood. Craniosynostosis and papilledema may accompany the infantile and childhood forms. There are six reported cases of craniosynostosis and papilledema in HPP; however, none contain ophthalmic follow-up. We report our experience with three patients with infantile HPP, craniosynostosis, and papilledema.

**Methods:** Patients received comprehensive ophthalmic examination and follow-up while receiving treatment for complications of infantile HPP.

**Results:** A 5.5 month old girl was diagnosed with HPP (compound heterozygote: c.1327G>T, p.Ala443Ser; c.1471G>A, p.Gly491Arg), and with craniosynostosis at six months of age. On ophthalmic examination, 3+ papilledema was found. Two and a half months after cranial vault expansion, papilledema worsened, and a second cranial vault expansion was performed. Four months after the second procedure, the papilledema had resolved and the nerves were pink and healthy with normal visual behavior for age. There has been no recurrence 7 months postoperatively. A 27 month old male was referred for management of complications of HPP (homozygous c.293C>T, p.S98F). Craniosynostosis was found on clinical and radiologic examination and ophthalmologic consultation showed 2+ disc swelling bilaterally; cranial vault expansion was performed. Disc swelling resolved after 4.5 months, and 14 months after cranial vault expansion, the nerves remain pink and healthy with normal visual behavior. His sister (same mutation) was referred at 5.5 years. Infantile HPP was diagnosed at 8 months and nystagmus was noted at 3.5 years. On examination, she had craniosynostosis, bilateral optic atrophy, roving nystagmus, and left exotropia. A cranial vault expansion was performed. At 6.5 years old, acuity was 20/250 OD and hand motions OS, a red green color vision defect, and constricted fields. The nerves remain atrophic.

**Conclusions:** Untreated papilledema resulted in visual impairment, but prompt treatment of elevated intracranial pressure associated with craniosynostosis in HPP leads to resolution of papilledema over several months’ time.

**Commercial Relationships:** Constance E. West, None; Robert B. Hufnagel, None; Howard M. Saal, None