**Investigating the Cerebrospinal Fluid Pressure Waveform and Volume Pressure Response in Idiopathic Intracranial Hypertension**

**Purpose:** To characterize tissue compliance and the cerebrospinal fluid (CSF) pressure waveform in idiopathic intracranial hypertension (IIH).

**Methods:** Twelve subjects who met the Modified Dandy Criteria, including papilledema and visual field loss, received an ultrasound guided lumbar puncture (LP) where CSF pressure (CSFP) was recorded at each increment of CSF removal. CSF pressure at each increment of volume removed was plotted (Figure 1) and used to calculate tissue compliance for each subject. Six subjects had their CSFP waveform recorded with an electronic transducer. BMI, mean CSFP, and cerebral perfusion pressure (CPP) were also calculated.

**Results:** For all subjects, the average opening and closing CSFP was 32.58±6.04 mmHg (Range: 20 to 42 mmHg) and 13.43±2.53 mmHg (Range: 10 to 17 mmHg) respectively. Nine of the subjects had an average initial and final CPP of 50.60±13.51 mmHg (Range: 30 to 69 mmHg) and 105±10.82 mmHg (Range: 90 to 127 mmHg) respectively. Six of the subjects had an average initial and final Cerebral Pulse Amplitude (CPA) of 6.81±2.01 mmHg (Range: 4.37 to 9.64 mmHg) and 1.28±.46 mmHg (Range: .79 to 1.79 mmHg) respectively. CSFP, CPA, and CPP were found to be significantly different (p < .05) before and after the LP. CSFP and CPA decreased after the LP, while CPP increased. The cerebrospinal tissue compliance significantly increased (P < .05) post-LP, with decreased CSFP. CPA and CSFP were significantly positively correlated (Figure 2).

**Conclusions:** Both low cerebrospinal tissue compliance (at high CSFP) and high cerebrospinal tissue compliance (at low CSFP) regions were determined for each subject. The CSFP waveform in IIH was characterized as a function of volume, and CPA was found to be influenced by the magnitude of CSFP and cerebrospinal tissue compliance. Future studies will investigate how cerebrospinal tissue compliance may correlate to the symptoms and response to therapy in IIH subjects.

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**Commercial Relationships:**
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pressure (EVP), intraocular pressure (IOP) and retinal vein diameter (RVD) of the eye. EVP measurement is routine in aqueous humor dynamics glaucoma research. EVP has a predicted 1:1 correlation with IOP.

**Methods:** A lumbar drain was used to vary ICP in 5 female domestic pigs in this established non-survival animal model. A parenchymal monitor (Integra Camino, USA) was inserted for accurate ICP monitoring. ICP was varied using normal saline infusion in 5 mmHg increments. The following parameters were measured at baseline and at all ICP increments after 10 minutes of ICP stability. 1) Right eye: IOP (pneumotonometry), EVP (venomanometry) 2) dilated left eye: OCT of optic nerve (Heidelberg Engineering, Germany). Retinal veins were identified on the OCT composite image and 2 independent graders measured RVD of 2 veins/pig. The univariate correlation of EVP, IOP and RVD with ICP changes was evaluated using linear mixed models with random intercepts.

**Results:** The baseline ICP was 4.5 mmHg (range 1.5-8 mmHg). Maximum stable ICP achieved ranged from 13-40 mmHg. The EVP increased with increase in ICP (β=0.26, p = 0.01). IOP increased with increase in ICP (β=0.36, p=0.0002). There was a subjective increase in anterior segment congestion and venous congestion on examination and photography. There was an increase in retinal vein diameter thickness with ICP; this was correlated with EVP (β=6.12, p=0.05).

**Conclusions:** EVP is a novel biomarker for increased ICP. Acute ICP increase causes increased ocular venous congestion resulting in significant increase in EVP and IOP in a pig model. The increased EVP is correlated to RVD. This increased congestion could potentially be due to an increase in cavernous sinus pressure which drains the central retinal vein and episcleral veins.

**Program Number:** 4306
**Presentation Time:** 11:30 AM–11:45 AM
**Optic nerve sheath ultrasonography identifies increased intracranial pressure in a diverse pediatric population: A comparative study**

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**Purpose:** Identification of increased intracranial pressure (ICP) in the pediatric population, especially infants, can be challenging. This retrospective, observational clinical study tests the hypothesis that optic nerve sheath (ONS) ultrasonography can be reliably used to help identify such cases. We seek to characterize trends in optic nerve sheath diameter (ONSD) by age, race, and sex, and to establish reference values.

**Methods:** A retrospective chart review was conducted on patients age 0 to 18 years (n=1,112 eyes) at a single institution who underwent B-scan ultrasonography of the ONS. These patients were referred to the ophthalmology clinic by pediatricians and neurologists for a variety of reasons, most commonly headache. If a lumbar puncture was performed, opening pressures (OP) were also recorded. Student’s t test, ANOVA, and regression modeling was used for statistical analysis. A receiver operating characteristic (ROC) curve was generated.

**Results:** In the multiple regression model, age was the most predictive factor of ONSD. The ONSD for normal children measured 5.44 ± 0.04 mm, versus 5.81 ± 0.72 mm in patients clinically diagnosed with increased ICP (P<0.0001). In patients with a high OP >20 cm H2O, the OSND was 6.34 ± 0.70 mm. Males had an ONSD of 5.54 ± 0.77 mm, larger than that of females (5.35 ± 0.63 mm, P=0.006). Whites had a 0.18 mm larger ONSD than blacks (5.52 ± 0.68 mm vs 5.34 ± 0.74 mm, P=0.016). There was no difference between right and left ONSD (P=0.85). The fastest growth in ONSD occurred in the first six months of life (R2=.65, R2=.42, P=0.0008), and the strongest differences, determined by Tukey’s method, were between the 0-18 month and post 18 month age groups. For patients less than 18 months of age, an ONSD of 5.0 mm had a

**Program Number:** 11402
**Presentation Time:** 11:30 AM–11:45 AM
**Identification of increased intracranial pressure (ICP) in the pediatric population: A comparative study**

*Deepta A. Ghate.* Nebraska Research Initiative 2015, Research to prevent blindness.
sensitivity of 100% for idiopathic increased ICP, and a specificity of 74% (AUC=0.90, P=0.0027). In patients older than 18 months, a cutoff value of 5.5 mm had a sensitivity of 79% and specificity of 51% (AUC=0.70, P=0.0001).

Conclusions: ONSD ultrasonography is a cost effective, atraumatic means of screening for elevated ICP in pediatric patients in an office setting. Age appropriate ONSD cut-off values can be applied to monitor suspected cases of increased ICP, and to determine whether further invasive diagnostic procedures such as MRI or lumbar puncture are warranted.

Commercial Relationships: Isabelle Dortonne, None; Clayton Stevens, None; Robert Gordon, None

Program Number: 4307
Presentation Time: 11:45 AM–12:00 PM
Optic Nerve Head Edema (ONHE) Among Patients Presenting to the Emergency Department In The FOTO-ED Study (Fundus photography vs. Ophthalmoscopy Trial Outcomes in the Emergency Department)

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Purpose: The FOTO-ED study showed that non-mydriatic retinal photography in the emergency department (ED) is feasible and may improve patient care and outcomes when systematically performed in patients with a chief complaint of headache, neurologic deficit, visual loss, or elevated blood pressure (BP). Finding ONHE is particularly important in this patient population. The purpose of this study was to describe the characteristics of the patients diagnosed with ONHE in FOTO-ED phases 1-3 and test the hypothesis that presence of disc edema alters the management of the patients presenting to ED.

Methods: Cross-sectional analysis of patients diagnosed with ONHE in all 3 phases of the prospective FOTO-ED study. The ONHE subgroup was compared to the non-ONHE group using logistic regression.

Results: The FOTO-ED studies included 1429 patients, among whom 36 (2.5%, 95% CI:1.8-3.5%) had ONHE [median age, 31 (IQR:27-40), women, 71.4%, African-Americans, 77.8%]. ONHE was bilateral in 26/36 and unilateral in 10/36 patients. Chief complaints included headaches (18/36), acute visual deficit (10/36), acute neurological deficit (4/36), elevated BP (2/36), both headaches and acute visual deficit (2/36). Final diagnoses were IIIH (18/36), optic neuritis (3/36), CSF shunt malfunction/infection (3/36); 2 each with brain tumor, non-arteritic ischemic optic neuropathy, cerebral venous sinus thrombosis, and malignant hypertension; and 1 each with meningitis, cerebral infarction, neurosarcoidosis, and retinopathy. 15/36 patients were sent to the ED with a diagnosis of ONHE already made by the referring physician; fundus photographs were the first to establish ONHE in 21/36 (58%) while in the ED; the ED providers identified the presence of ONHE in only 5/21 (23.8%) of these patients. Knowledge of ONHE led to a change in final diagnosis for 10/36 patients.

Conclusions: One in 40 patients (2.5%) presenting to the ED with a chief complaint of headache, neurologic deficit, visual loss, or elevated BP had ONHE. Our results are consistent with the hypothesis that the identification of ONHE altered the patient disposition and contributed to the final diagnosis, confirming the importance of funduscopic examination in the ED.

Commercial Relationships: Virender Sachdeva, None; Caroline Vasseneix, None; Rabih Hage, None; Samuel Bidot, None; Lindsay C. Clough, None; David W. Wright, None; Bea B. Bruce, None; Valerie Bioussé, None; Nancy J. Newman, None

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Clinical Trial: NCT00873613

Program Number: 4308
Presentation Time: 12:00 PM–12:15 PM
Three-Dimensional Bruch’s Membrane Shape Change Over Time with Acetazolamide Treatment in the Idiopathic Intracranial Hypertension Treatment Trial (IIHTT)

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Purpose: We demonstrated that the Bruch’s membrane (BM) shape change from toward the vitreous to away from vitreous over time is more significant with treatment of diet+acetazolamide (ACZ) than diet+placebo using a 2D BM shape model in IIHTT; next, we extended the 2D BM shape model into a 3D version (Wang et al. ARVO 2015, 2016). In this work, after applying the 3D shape model to the IIHTT data, we further analyzed the 3D shape change over time and the treatment effect.

Methods: The 3D BM and 2D opening (BMO) contour was first segmented in each spectral-domain optical coherence tomography (SD-OCT) optic-nerve-head (ONH) volumetric scan using our prior approach. Next, on the pre-segmented BM surface, 288 landmarks were placed along the obtained BMO contour; for every 10⁶, eight equidistant landmarks were chosen covering 1.5 mm in the radial direction. The flowchart is shown in Fig. 1. By applying principal component analysis (PCA), the first component coefficient was computed to quantify the BM shape change towards/away from the vitreous in 3D (Fig. 2a).

Results: In the IIHTT OCT sub-study, of the 116 right eyes used in the IIHTT data, we further analyzed the 3D shape change over time and the treatment effect. The 3D BM opening (BMO) contour was first segmented in each spectral-domain optical coherence tomography (SD-OCT) optic-nerve-head (ONH) volumetric scan using our prior approach. Next, on the pre-segmented BM surface, 288 landmarks were placed along the obtained BMO contour; for every 10⁶, eight equidistant landmarks were chosen covering 1.5 mm in the radial direction. The flowchart is shown in Fig. 1. By applying principal component analysis (PCA), the first component coefficient was computed to quantify the BM shape change towards/away from the vitreous in 3D (Fig. 2a).

Conclusions: BM shape measures in 2D and 3D are highly correlated (p=0.81, p<0.01) and have been shown as potential biomarkers of successful treatment of papiledema. The 3D shape measure, compared to the 2D version, has an additional advantage of consolidating 3D information. Developing a fully-automated method and incorporating more principal components from the 3D BM shape models constitute future efforts.
Fig. 1 Flowchart of generating 3D BM shape models

Fig. 2 (a) 3D BM shape model variations (b) the 3D shape measures in ACZ/placebo groups at baseline, three and six months

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Clinical Trial: NCT01003639
Effects of acute intracranial pressure change on human and pig optic nerve head using optical coherence tomography
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Purpose: We assessed the effect of acute intracranial pressure (ICP) decrease after lumbar puncture (LP) in humans and acute ICP increase in a pig model on the optic nerve head (ONH) morphology. We hypothesized that acute ICP increase would lead to anterior shift of lamina cribrosa (LC) and acute ICP decrease a posterior LC shift.

Methods: LP study: ONH imaging (12 enhanced depth imaging (EDI) radial sections; Cirrus HD-OCT), intraocular pressure (IOP), CSF opening (OP) and closing (CP) pressures were obtained in 19 subjects before and after LP. Bruch’s membrane opening diameter (BMOD) and anterior lamina cribrosa depth (ALCD) were measured by 2 graders for all 12 radial sections after importing the images into Image J software. Repeated measures ANOVA evaluated differences in BMOD and ALCD before and after LP.

Pig study: ICP was increased in 5 mm Hg increments using lumbar drain in 3 anesthetized pigs, while ICP was monitored by a parenchymal monitor (Integra Camino). At each ICP level (stabilized to ±2 mm Hg for 10 minutes), ONH imaging of right eye (12 EDI radial sections; Spectralis OCT), IOP of left eye (Pneumotonometry) were obtained. ONH images were graded as above. Change for each variable was calculated and modeled as a fixed effect for longitudinal data. Slopes were evaluated for statistical significance to determine if changes in ICP were associated with changes in BMOD and ALCD.

Results: LP study: Mean CSF-OP was 15.5 mm Hg (range: 4-31 mm Hg); mean ICP change was 8 mm Hg (range: 2.6-17.7 mm Hg).

There was a small, statistically insignificant IOP decrease after LP in IIH patients (1.2 mm Hg) vs. non-IIH (0.3 mm Hg).

Pig study: Baseline ICP was 4.5 mm Hg (range 1.5-8 mm Hg) and maximal stable ICP ranged from 18-32 mm Hg. Acute ICP elevation led to IOP increase in pig models (discussed separately).

In both studies, no significant changes of BMOD and ALCD were seen in all 12 radial sections following ICP changes.

Conclusions: Acute ICP changes did not produce measurable changes of ONH morphology in humans and pig. The LC appears resistant to significant displacements despite large changes of ICP possibly due to compensatory mechanisms such as IOP changes. Study limitations include small sample size and/or small effect size.

Measurement of BMOD and ACLD of ONH images in Image J in pigs (c- baseline; d- raised ICP)

Gaze-evoked deformations in optic nerve head drusen
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Purpose: We recently described gaze-evoked, “seesaw” deformations of the peripapillary basement membrane-layer (ppBM-layer) in patients with papilledema, ischemic optic neuropathy (AION) and normals.1 The deformations in papilledema were large and presumably due to gaze-induced hydraulic shifts of cerebrospinal fluid against the scleral flange. In AION and normals the deformations were small, temporal to the basement membrane opening (BMO) and presumably due to the tensile tethering of the globe by the optic nerve sheath in adduction.2,3 This study examines the effects of eye position on the shape of the ppBM-layer in patients with optic nerve head drusen (ONHD).

Methods: We examined registered 9 mm SD-OCT axial-rasters from 20 patients with optic disc drusen. Images were obtained with head rotated so that eyes were positioned at 10-15° adduction and 30-40° abduction. Geometric Morphometric shape analysis, previously described4,5, was used to analyse the ppBM-layer spanning 2500 microns on each side of the BMO.

Results: There was a statistically significant difference in the shape of the ppBM-layer between abduction and adduction (p=0.01, permutation) characterized by an alternating deformational tilt. On adduction there was a relative posterior displacement of the temporal side with a slight anterior displacement of the nasal side. The reverse pattern occurred in abduction. The magnitude of the deformations in ONHD were similar to those described previously in AION and normals; and substantially smaller than papilledema.

Conclusions: The BMO is a high stress environment. Ocular ductions induce multiple complex modes of strain (i.e. shearing,
compression, extension) within and around the ONH that can potentially generate friction between the soft tissues of the ONH (e.g. axons, glial cells, blood vessels, border tissues) and the rigid, sometimes irregular margins of ONHD. The cumulative traumatic effects of repetitive motion from eye movements may be a contributory factor in progressive loss of axons, hemorrhages, vascular occlusions and neovascular membranes that occur in patients with optic nerve head drusen.


Commercial Relationships: Patrick A. Sibony