JAMA Ophthalmology | Original Investigation

Using Optical Coherence Tomography Measures as Surrogates for Raised Intracranial Pressure in Idiopathic Intracranial Hypertension

Vivek Vijay, MD; Susan P. Mollan, MD; James L. Mitchell, MD; Edward Bilton, MD; Zerin Alimajstorovic, PhD; Keira A. Markey, MD, PhD; Anthony Fong, MD; Jessica K. Walker, MD; Hannah S. Lyons, MD; Andreas Yiangou, MD; Georgios Tsermoulas, MD; Kristian Brock, PhD; Alexandra J. Sinclair, MD, PhD

IMPORTANCE There is an unmet need for noninvasive biomarkers of intracranial pressure (ICP), which manifests as papilledema that can be quantified by optical coherence tomography (OCT) imaging.

OBJECTIVE To determine whether OCT of the optic nerve head in papilledema could act as a surrogate measure of ICP.

DESIGN, SETTING, AND PARTICIPANTS This longitudinal cohort study used data collected from 3 randomized clinical trials that were conducted between April 1, 2014, and August 1, 2019. Participants who were female and had active idiopathic intracranial hypertension were enrolled from 5 National Health Service hospitals in the UK. Automated perimetry and OCT imaging was followed immediately by ICP measurement on the same day. Cohort 1 used continuous sitting telemetric ICP monitoring (Raumedic Neurovent P-tel device) on 1 visit. Cohort 2 was evaluated at baseline and after 3, 12, and 24 months and underwent lumbar puncture assessment of ICP.

MAIN OUTCOMES AND MEASURES Optical coherence tomography measures of the optic nerve head and macula were correlated with ICP levels, Frisén grading, and perimetric mean deviation. The OCT protocol included peripapillary retinal nerve fiber layer, optic nerve head, and macular volume scans (Spectralis [Heidelberg Engineering]). All scans were validated for quality and resegmented manually when required.

RESULTS A total of 104 women were recruited. Among cohort 1 (n = 15; mean [SD] age, 28.2 [9.4] years), the range of OCT protocols were evaluated, and optic nerve head central thickness was found to be most closely associated with ICP (right eye: r = 0.60; P = .02; left eye: r = 0.73; P = .002). Subsequently, findings from cohort 2 (n = 89; mean [SD] age, 31.8 [7.5] years) confirmed the correlation between central thickness and ICP longitudinally (12 and 24 months). Finally, bootstrap surrogacy analysis noted a positive association between central thickness and change in ICP at all points (eg, at 12 months, an decrease in central thickness of 50 µm was associated with a decrease in ICP of 5 cm H_2O).

CONCLUSIONS AND RELEVANCE In this study, optic nerve head volume measures on OCT (particularly central thickness) reproducibly correlated with ICP and surrogacy analysis demonstrated its ability to inform ICP changes. These data suggest that OCT has the utility to not only monitor papilledema but also noninvasively prognosticate ICP levels in idiopathic intracranial hypertension.

Supplemental content

Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Author: Alexandra J. Sinclair, MD, PhD, Metabolic Neurology, Institute of Metabolism and Systems Research, College of Medical and Dental Sciences, University of Birmingham, Birmingham B15 2TT, UK (a.b.sinclair@bham.ac.uk).

JAMA Ophthalmol. doi:10.1001/jamaophthalmol.2020.4242
Published online October 22, 2020.

Lumbar puncture (LP) is the most common way currently used to measure intracranial pressure (ICP). There are considerable drawbacks in this invasive assessment, including complications[1,2] and a negative patient experience.[3] Telemetric ICP devices provide more accurate and comprehensive assessments of ICP and are increasing our understanding of cerebrospinal fluid dynamics, but these require formal placement.[4] Determining a noninvasive measure of ICP would be a key step forward in patient management of many conditions, such as traumatic brain injury and spaceflight associated neuro-ocular syndrome, among other serious intracranial conditions, where the gold standard for ICP measurement is an external ventricular drain with known complications.[4,5]

On the surface, optical coherence tomography (OCT) imaging of the optic nerve head appears to be a valuable clinical tool used globally in ophthalmology clinics for the longitudinal monitoring of papilledema in conditions such as idiopathic intracranial hypertension (IIH)[6] and spaceflight associated neuro-ocular syndrome.[7] Optical coherence tomography measures correlate with the severity of papilledema, as assessed by experts[8] using Frisén papilledema grading.[9] However, there appears to be a more complicated association between OCT parameters, papilledema grade, and measured ICP.[10-13] Most investigators have used custom-made algorithms to demonstrate features in OCT imaging that may reflect ICP, and although these pave the way for development of proprietary software, they currently are limited in the generalizability of their findings to the real-world setting.[12,13] Optical coherence tomography measures of the peripapillary retinal structure have previously been correlated with invasively measured ICP in a pediatric cohort at the time of neurosurgery.[14] The aim of this study was to determine a surrogate measure of ICP by using OCT imaging with standard analysis software, so the results could be readily transferable into routine clinical practice.

Key Points

Question Do results of optical coherence tomography of papilledema correlate with intracranial pressure levels in idiopathic intracranial hypertension?

Findings This 2-stage analysis of 104 participants' optic nerve head volume measures of central thickness, central volume, maximum height (any point), and maximum height (central slice) all correlated with intracranial pressure measured either by telemetry or lumbar puncture. Macular ganglion cell layer volume also correlated with visual field mean deviation at 12 months.

Meaning Optical coherence tomography imaging has the potential to be a noninvasive measure of intracranial pressure; central thickness values were associated with change in intracranial pressure at 12 and 24 months.

Methods

Study Population

Women with IIH aged 18 to 45 years were recruited from the following institutions: Queen Elizabeth Hospital, University Hospital Birmingham National Health Service (NHS) Foundation Trust, Birmingham, UK; The Walton Centre, Liverpool, UK; and Manchester Royal Eye Hospital, Manchester University NHS Foundation Trust, Manchester, UK; Queen Elizabeth Hospital, Glasgow, UK; and the Royal Devon and Exeter NHS Foundation Trust, Exeter, UK. Patients were reimbursed for travel and childcare costs. Patients with IIH were diagnosed according to the internationally accepted diagnostic criteria[15] and included only if they had active disease with ongoing papilledema (Frisén grade ≥1) in at least 1 eye, and cerebrospinal fluid pressure greater than 25 cm H_2O at enrollment (eFigure 1 in the Supplement). Those with an alternate ocular diagnosis of visual acuity loss were excluded. Automated perimetry (Swedish Interactive Threshold Algorithm standard 24-2 strategy, Humphrey Visual Field Analyzer [Carl Zeiss Meditec]) was performed on the same day as the OCT scan protocol, prior to ICP measurement.

Standard Protocol Approvals and Patient Consent

Written informed consent was obtained from each participant as a condition of their inclusion in the original randomized clinical trial. The research was approved by the National Research Ethics Committee (West Midlands-The Black Country and the York and Humber/Leeds West). This study followed the tenets of the Declaration of Helsinki.

Evaluations

Cohort 1

Patients with IIH were recruited into an interventional trial that required a Raumedic Neurovent P-tel device (Raumedic AG) implanted under general anesthesia as part of the research protocol, for recording over a 12-week period. No immediate complications were noted. Prior to enrollment, participants were required to have papilledema; this was graded by a neuro-ophthalmologist through a dilated fundus slitlamp examination. Assessments of ICP were captured 1 week after telemeter placement. For each ICP measurement (in the standing, sitting, and supine positions), ICP was allowed to settle and was measured for 5 minutes at 1 Hz. The mean ICP was then calculated over this period. Patients were also requested to have a period of prolonged home ICP monitoring initiated on waking and continuing for up to 24 hours (reflecting ICP during the activities of normal daily living). Data were evaluated in those with prolonged monitoring for longer than 5 hours, and the mean ICP was calculated. This cohort was part of a broader trial (isrctn.org Identifier: ISRCTN12678718), but only baseline preintervention data were used for this study.[16]

Cohort 2

Participants in cohort 2 were drawn from 2 intervention trials conducted over the same period, with analogous recruitment criteria and schedules of events (including the OCT imaging protocol).[17-19] Patients with IIH in cohort 2 had ICP assessed by ultrasonography-guided LP on the same day, after automated perimetry and OCT scanning. This cohort also had color fundal photographs (Topcon) obtained at each study visit. Photographs were evaluated by 3 neuro-ophthalmic specialists

Table 1. Baseline Characteristics

Characteristic	Mean (SD)		
	All	Cohort 1 (telemetric intracranial pressure)	Cohort 2 (lumbar puncture)
Total, No.	104	15	89
Age, y	31.3 (7.9)	28.2 (9.4)	31.8 (7.5)
BMI	42.1 (9.2)	38.1 (6.2)	42.7 (9.5)
Mean deviation, median (range), dB	−1.88 (−24.76 to 6.9)	−0.89 (−5.66 to 4.47)	−2.0 (−24.76 to 6.9)
Intracranial pressure, cm H_2O	33.6 (4.9)[a]	29.9 (6.7)[a]	34.2 (5.6)
Peripapillary retinal nerve fiber layer thickness thickness, µm	137 (57)	166 (80)	133 (53)
Optic nerve head central thickness, µm	650 (196)	731 (144)	634 (203)
Macular ganglion cell layer global volume, mm^3	1.1 (0.1)	1.09 (0.1)	1.1 (0.1)

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared).

[a] Intracranial pressure measurements have been made comparable by converting the cohort value of 1 mm Hg in the supine position to cm H_2O.

(S.P.M. and 2 nonauthors) to determine Frisén grading.[9] Where there was disagreement in the grading, all 3 reviewed the photographs together and provided a final consensus grading. Patients were followed up at 3, 12, and 24 months. Data for both cohorts were collected between April 1, 2014, and August 1, 2019.

OCT

The OCT methodology and results are reported in line with the Advised Protocol for OCT Study Terminology and Elements (APOSTEL) reporting recommendations.[20] All OCT imaging was performed using a Spectralis OCT system (Heidelberg Engineering). Exclusion criteria included ophthalmologic and systemic diseases with the potential to influence retinal morphology, as defined by the obvious problems (including violation of the protocol), poor signal strength (defined as <15 dB), wrong centration of scan, algorithm failure, retinal pathology other than multiple sclerosis, illumination, and beam placement (OSCAR-IB) criteria, applied at the eye level.[21,22] Mean retinal nerve fiber layer (RNFL) thickness was calculated along the circumference of a circle with a diameter of 3.45 mm that was centered on the optic disc (eMethods 1 and eFigure 2 in the Supplement). To enable the results to be clinic ready, all data points evaluated reflected those generated by the proprietary software. No bespoke scanning-analysis programs were applied.

Statistical Analysis

Descriptive statistics were used to compare demographic characteristics. Statistical analysis was performed using GraphPad, version 8.3 (GraphPad Software). Means and SDs are provided for normally distributed variables, and medians and ranges are provided for nonnormally distributed variables. Pearson correlation coefficients were computed when the variables were normally distributed and all assumptions were met, with Spearman rank correlation used in other cases. Values were deemed statistically significant at $P < .05$. Missing data, attributable to any absence of the complete scanning protocol (for example, cases in which some of the OCT data were captured and then a patient did not tolerate the prolonged scanning) were excluded from the analysis.

In cohort 1, initial exploratory analysis involved evaluating a priori hypothesized associations between OCT measures and ICP; these were assessed using scatterplots and calculating correlation coefficients. No corrections were made for multiple comparisons, because this initial exploratory analysis sought to identify trends in the data between ICP and OCT that would then be further evaluated in cohort 2.

In cohort 2, the leading OCT parameter from cohort 1, with the optimal correlation to ICP, was evaluated over a time horizon of follow-up visits (at 3, 12, and 24 months). At each point, the correlation between ICP and the OCT parameter was evaluated for each eye. The association between the OCT parameters (leading OCT parameter associated with ICP; the OCT ganglion cell layer [GCL] global volume) and the visual field mean deviation (MD) was also assessed through calculating correlation coefficients over the time horizons. Assessment by surrogacy methods is shown in eMethods 2 in the Supplement.

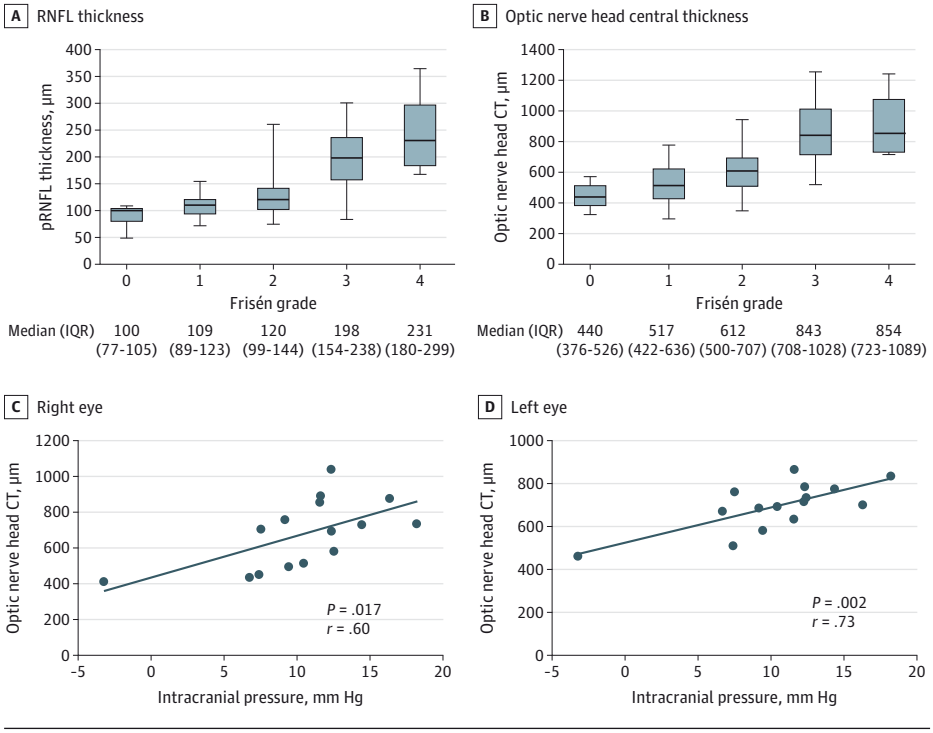
Results

A total of 104 patients with IIH, all female, were included (cohort 1: n = 15; mean [SD] age, 28.2 [9.4] years; cohort 2: n = 89; mean [SD] age, 31.8 [7.5] years) (**Table 1**). At baseline, cohort 1 had more severe optic disc swelling at baseline. This was reflected in a mean RNFL thickness (both eyes) of 157 (range, 70-337) µm in cohort 1, compared with 133 (range, 48-364) µm in cohort 2 (Table 1). Baseline median visual field MD (both eyes) was −0.89 (range, −5.66 to 4.47) dB in cohort 1 and −2.0 (range, −24.76 to 6.9) dB in cohort 2. Mean (SD) ICP in cohort 1 while supine was 22.0 (4.9) mm Hg, equivalent to 29.9 (6.7) cm H_2O. In cohort 2, the mean (SD) ICP as measured by LP opening pressure was 34.2 (5.6) cm H_2O.

Overall, 1211 of 1386 scans were included in the analysis. A total of 139 scans were missing (at any point), and following quality control assessment of the OCT images, a further 36 scans were excluded. Therefore, 12.6% of all OCT scan images were either classified as excluded or missing (eTable 1 in the Supplement).

Initially, the association between papilledema severity, according to Frisén grading, to the OCT parameters (**Figure 1**A and Figure 1B) and MD were analyzed. A strong correlation between Frisén grading and both the RNFL (r = 0.4655; $P < .001$) and optical nerve head central thickness (ONH CT) ($r = 0.5728$; $P < .001$) was noted. Frisén grading was also associated with

Figure 1. Distribution of Retinal Nerve Fiber Layer (RNFL) and Optical Nerve Head Central Thickness (ONH CT) Values per Frisén Grade and Correlation of Telemetric Intracranial Pressure (ICP) With RNFL and ONH CT



A and B, Box-and-whisker plots showing medians, ranges, and interquartile ranges (IQRs) of RNFL thickness (A) and ONH CT (B) per Frisén grade, with medians (IQRs) documented numerically for each Frisén grade. C and D, Scatter plots of the mean telemetric ICP values (sat) and optic nerve head central thickness values. Optic nerve head CT is significantly correlated with ICP (B, right eye: $r = 0.60$; $P = .02$; C, left eye, $r = 0.73$; $P = .002$). pRNFL indicates peripapillary retinal nerve fiber layer.

the visual field MD ($r = -0.2722$; $P = .003$) but not with ICP at baseline.

Measurements of Telemetric ICP

Initially, cohort 1 was evaluated using highly accurate telemetric ICP measurements. All patients had ICP measurements evaluated in the sitting, standing, and supine positions. Prolonged ICP monitoring was available in 8 of 15 participants (53%) during activities of daily living (mean duration of prolonged ICP recording, 13.6 [range, 5-21] hours). Prolonged ICP monitoring values were akin to ICP measures in the sitting and standing positions but 2-fold lower than supine ICP (prolonged, mean [SD], 11.8 [2.6] mm Hg; sitting, mean [SD], 8.9 [5.5] mm Hg; supine, mean [SD], 22.0 [3.1] mm Hg; standing, mean [SD], 8.7 [3.2] mm Hg) (eFigure 3 in the Supplement). Sitting mean (SD) ICP values were therefore chosen, because not only are OCT scans acquired in the sitting position, but as was shown here, they were representative of prolonged mean ICP (eFigure 3 in the Supplement).

Association of OCT Measurements to ICP

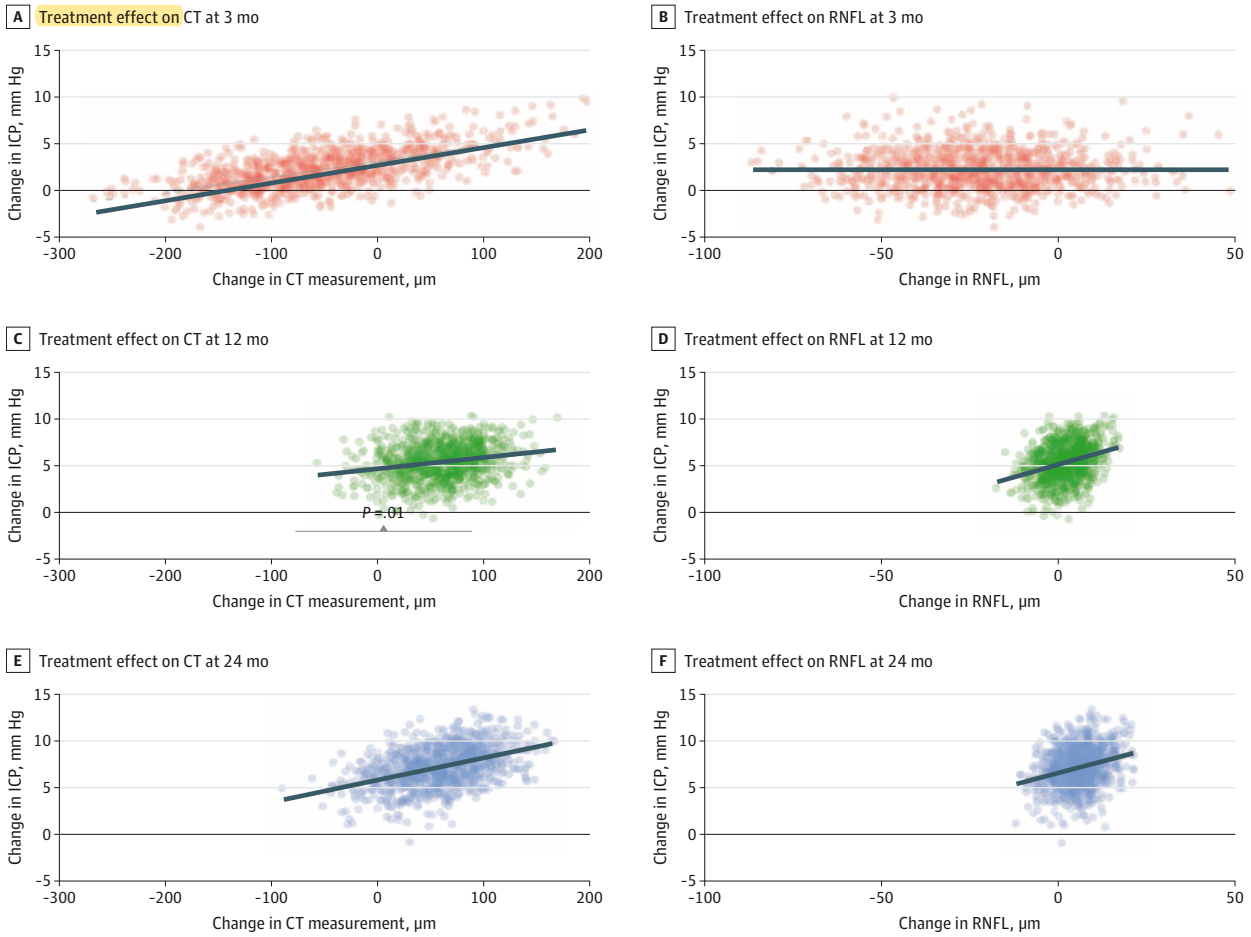
Of all the OCT scan proprietary measures collated from the 3 protocols obtained (RNFL, ONH, and macula volume) (eFigure 2 in the Supplement), there was no correlation of RNFL, any of the macula volume components, and most ONH volume individual components with ICP in cohort 1. Within the measures of the ONH volume (maximum height central [MHC], maximum height anywhere [MH], central thickness [CT], and central volume [CV]), all correlated with ICP (right eye: MH, $r = 0.5221$; $P = .046$; MHC, $r = 0.5600$; $P = .03$; CV, $r = 0.6059$; $P = .02$; CT, $r = 0.6034$; $P = .017$; left eye: MH, $r = 0.6970$; $P = .004$; MHC, $r = 0.6693$; $P = .006$; CV, $r = 0.7267$; $P = .002$; CT, $r = 0.7275$; $P = .002$) (Figure 1C and Figure 1D and eTable 2 in the Supplement).

The ONH CT was chosen pragmatically to evaluate the association with ICP in cohort 2 (a larger cohort with ICP measured using LP), because it was a whole integer. Intracranial pressure correlated with ONH CT with increasing strength across disease duration (baseline: right eye: $r = 0.21$; $P = .08$; left eye, $r = 0.28$; $P = .02$; 12 months: right eye: $r = 0.28$; $P = .05$; left eye, $r = 0.36$; $P = .01$; 24 months: right eye, $r = 0.46$; $P = .01$; left eye, $r = 0.46$; $P = .01$) (eFigure 4 and eTable 3 in the Supplement). There was an inconsistent and nonsignificant association between RNFL and ICP (eTable 3 in the Supplement).

Surrogacy of OCT Measures With ICP

Surrogacy analysis identified a positive association between ICP and ONH CT at 3, 12, and 24 months, with a larger change in intracranial pressure for CT coinciding with a larger change in intracranial pressure for ICP (**Figure 2**A). The surrogacy analysis data points (Figure 2) represent trial outcomes, each as likely as any other. Thus, the location and dispersion of the points provides evidence on the coincident nature of the change in ICP. Thus, surrogacy was observed at all points (3, 12 and 24 months). Using the surrogacy analysis plots, changes in ICP can be estimated from changes in ONH CT (**Table 2**); for example, at 12 months' follow-up, the change in ONH CT of 50 µm is associated with a change in ICP of 5 cm H_2O in (Table 2), and at 24 months, a change of 50 µm is associated with an ICP

Figure 2. Bootstrap Surrogacy Analysis of Intracranial Pressure (ICP) and Optical Coherence Tomography (OCT) Outcomes



The x-axis reflects changes in OCT with change in ICP on the y-axis. The lines are simple linear regressions, and the shaded regions are 95% CIs of the mean. Changes in ICP are plotted at 3, 12, and 24 months. Each positive value represents improvement (ie, reduction in ICP and OCT); the larger the angle of the slope, the greater the association. A, Optical nerve head central thickness on the y-axis with a positive association between parameters observed over the time horizons. B, Retinal nerve fiber layer on the y-axis with seemingly random dispersion of data points, indicating a lack of association between retinal nerve fiber layer and ICP.

Table 2. Prognosticating Intracranial Pressure (ICP) From Optical Coherence Tomography Central Thickness, as Measured on the Optic Nerve Head Volume Scan[a]

Time, mo	Change in optic nerve head volume central thickness measure, µm	Change in mean intracranial pressure (95% CI), cm H_2O
12	50	5.0 (1.4-8.3)
12	100	5.9 (1.9-9.1)
24	50	6.5 (2.3-9.9)
24	100	8.5 (4.8-12.6)

[a] Changes in ICP prognosticated by bootstrap surrogacy analysis conditional on central thickness changes in ICP. A reduction in central thickness of 100 µm at 12 months is highly likely to be associated with a reduction in ICP at 12 months (mean decrease, 5.9 [95% CI, 1.9-9.1] cm H_2O). Similarly, observation of a reduction in central thickness of at least 50 µm at 24 months is highly likely to be associated with a reduction in ICP (mean decrease, 6.5 [95% CI, 2.3-9.9] cm H_2O).

change of 7 cm H_2O. Surrogacy analysis for RNFL for ICP was weaker (Figure 2B).

OCT GCL Analysis and ICP

The association between the OCT GCL analysis and ICP was evaluated, and there was no correlation noted over the study follow-up to 24 months; this included a lack of association when individual segments were evaluated on the inner and outer rings (superior, inferior, temporal, and nasal). Additionally, the extent of the papilledema measured by ONH CT was not associated with GCL loss over time.

OCT Analysis and Visual Field Perimetric MD

Axonal loss as measured by OCT GCL was positively correlated with visual field loss (MD) at baseline and 12 months (right eye: baseline, $r = 0.19$; $P = .13$; 12 months, $r = 0.42$; $P = .001$; left eye: baseline, $r = 0.31$; $P = .01$; 12 months, $r = 0.45$; $P < .001$) (eFigure 5 and eTable 4 in the Supplement). Insufficient data at 24 months prohibited analysis. The OCT measure of GCL was seen to act as a surrogate for MD, where the worse the GCL was, the lower the MD was (eFigure 5 in the Supplement).

Discussion

We believe there is an unmet clinical need for a noninvasive, objective measure of ICP. We conducted a longitudinal cohort study to define the potential for OCT measures to be a biomarker for ICP in patients with IIH. In cohort 1, using accurate telemetric ICP measures, we determined that the mean of a ICP measure from a 5-minute recording in the sitting position was equated with prolonged telemetric ICP measurements. Mean sitting telemetric ICP values were then demonstrated to correlate with OCT parameters. These were then investigated in turn in the larger cohort 2, where pragmatically, LP was used to measure ICP over a 24-month period. Our aims were to go further than just detecting the presence or absence of raised ICP, as others have reported.[23,24] One study[23] with telemetric ICP measures used a multiple linear regression model and confirmed a statistically significant association between ICP and spontaneous venous pulsation, as determined by observers grading the spontaneous venous pulsation on infrared videos, but did not assess the quantitative measures of the OCT scans. In a pediatric cohort,[14] when directly measuring ICP intraoperatively, the investigators were able to demonstrate OCT measures detecting raised ICP levels with 89% sensitivity and 62% specificity.

The OCT RNFL measurements in this study showed weak and inconsistent associations with ICP in both cohorts, as other investigators have found.[12] In the Idiopathic Intracranial Hypertension Treatment Trial (IIH TT), the OCT parameters of RNFL, total retinal volume, and ONH volume were significantly correlated with both Frisén grades and ICP levels (as measured by LP), but the correlation was stronger with Frisén grades (r >0.76) than with LP opening pressures (r >0.24).[11] There may be many reasons why this is the case: Frisén grading may take in additional clinical features for categorization or the standard circle sizes of both the ONH scans were not developed for optic nerve pathology and may be too large for the general anatomy of the ONH. In this study, the higher the Frisén grade, the less discriminating the RNFL value was (Figure 1A), and therefore this may not be as useful clinically to distinguish the worst degrees of papilledema.

A weak but significant correlation of the global ONH volume to ICP in people with IIH has been previously confirmed by others.[11,13,25] The strength of the association may have been limited by the size of the cohorts, use of LP opening pressure to measure ICP, time interval between LP, and procedures for capturing the OCT images. Certainly, Skau et al[26] and Wang et al[27] have concluded that OCT measures may be a more sensitive indicator of elevated ICP compared with papilledema grade, because a grader qualitatively classifies in a noncontinuous way, whereas OCT ONH parameters are quantified and continuous. Here, we found strong and consistent associations with OCT ONH volumetric measures of CT, CV, MH, and MHC and telemetric ICP (eTable 2 in the Supplement; Figure 1C and Figure 1D), which has not been investigated previously in this manner, to our knowledge. The estimated surrogacy associations between CT and ICP were positive at all 3 time horizons (3, 12, and 24 months). A reduction of ONH CT at least 50 µm at 12 or 24 months is highly likely to be associated with reductions in ICP on the order of 5 cm H_2O and 7 cm H_2O, respectively (Table 2).

Structure-function correlations are critically important, in that moving from visual field assessments to objective clinical tools, such as OCT, would be clearly advantageous for patients, clinicians, and researchers. Macular ganglion cell complex measurements have been found to be accurate and reliable biomarkers of visual function loss in a range of optic neuropathies, including glaucoma,[28] ischemia,[29] mitochondrial dysfunction,[30] and demyelination.[31] Monteiro et al[32] showed reduced sectoral and mean macular thickness, which correlated with visual field loss in patients with chronic papilledema. Here we found evidence of association between OCT-derived macular GCL global volume and visual field MD at baseline and 12 months (eTable 4 in the Supplement). Given the difficulty in patients with IIH of performance of automated visual fields,[33] there is may be potential for the OCT GCL to be used as a substitute because it correlated with visual function at later points.

Strengths

This is a large, well-characterized cohort of patients with IIH, drawn from 3 randomized clinical trials, ensuring highly standardized protocol of measurements. The study sample is representative of patients with IIH, with a case mix including those with active severe disease and those with milder disease activity (Table 1). It is to our knowledge the first study using precise, continuous telemetric ICP monitors to quantitatively assess the association between ICP and specific OCT parameters. We also pragmatically demonstrated these parameters using LP, as would be routinely done in clinical practice, in a larger cohort. Importantly, the OCT scans were obtained on the same day and prior to the ICP measurements. Use of the proprietary software means that the results of the study may be directly translatable into the clinical environment. Patients in cohort 2 received different interventions, which could have the potential to alter the trajectory of their disease; however, we consider this to be a strength, because it should not alter the associations between the parameters assessed.

Limitations

Ocular OCT is currently unable to distinguish between a reduction in thickness because of resolving edema from axonal loss. The segmentation of the layer algorithms have been shown to often fail in higher-grade papilledema.[8,34] In papilledema, identification of anatomical landmarks, such as Bruch membrane, which is required to produce measurements, may be hampered by lack of penetrance because of the elevation of the optic nerve and edema.[27] This may be why RNFL measures have few declared associations with ICP, because of failure in higher grades of papilledema. The use of surrogacy analysis should ideally have been conducted using trial data from multiple historical IIH trials, but unfortunately these seem not to exist. The bootstrapping resampling methods (eMethods 2 in the Supplement) was a pragmatic approach to enable a surrogacy assessment to be made.

Conclusions

As changes in ICP can be estimated from changes in the ONH volume parameters, further validation in a prospective real-world trial would be of immense interest. Future analysis should also include other OCT devices to see if the results of this study using the Heidelberg Spectralis could be generalized to other platforms. For situations in which tabletop OCT may not be viable, such as in the critical care setting or surgical theaters, mobile OCT devices are being trialed.[35]

Telemetric ICP, a gold-standard measure, has been used to identify candidate surrogate OCT markers reflecting ICP. These measures were then validated in a longitudinal study over 24 months. This study reports the use of OCT CT as a surrogate for ICP. Optical coherence tomography CT changes as ICP changes and may permit prognostication of ICP over time. Here, we have demonstrated the utility of OCT imaging measures that can be used to assess ICP and are directly translatable to routine clinical practice.

ARTICLE INFORMATION

Accepted for Publication: August 31, 2020.

Published Online: October 22, 2020. doi:10.1001/jamaophthalmol.2020.4242

Author Affiliations: Metabolic Neurology, Institute of Metabolism and Systems Research, College of Medical and Dental Sciences, University of Birmingham, Birmingham, UK (Vijay, Mitchell, Alimajstorovic, Markey, Yiangou, Sinclair); Centre for Endocrinology, Diabetes and Metabolism, Birmingham Health Partners, Birmingham, UK (Vijay, Mitchell, Yiangou, Sinclair); Department of Neurology, Queen Elizabeth Hospital, University Hospitals Birmingham NHS Foundation Trust, Birmingham, UK (Vijay, Mitchell, Markey, Yiangou, Sinclair); Birmingham Neuro-Ophthalmology, Ophthalmology Department, Queen Elizabeth Hospital, University Hospitals Birmingham NHS Foundation Trust, Birmingham, UK (Mollan, Bilton, Fong, Walker, Lyons); Department of Medicine, The University of Queensland, Herston, Queensland, Australia (Fong); Department of Neurosurgery, Queen Elizabeth Hospital, University Hospitals Birmingham NHS Foundation Trust, Birmingham, UK (Tsermoulas); Institute of Cancer and Genomic Sciences, University of Birmingham, Edgbaston, Birmingham, UK (Brock).

Author Contributions: Dr Sinclair had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Drs Vijay, Mollan, and Mitchell contributed equally.
Concept and design: Vijay, Mollan, Sinclair.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Vijay, Mollan, Alimajstorovic, Sinclair.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Vijay, Mitchell, Bilton, Alimajstorovic, Lyons, Brock, Sinclair.
Obtained funding: Mitchell, Sinclair.
Administrative, technical, or material support: Mollan, Mitchell, Markey, Walker, Yiangou, Sinclair.
Supervision: Mollan, Sinclair.

Conflict of Interest Disclosures: Dr Mollan reported personal fees from Heidelberg Engineering and advisory board fees from Invex Therapeutics during the conduct of the study and personal fees from Allergan, Santen, Sathera, Roche, Chugai, and Novartis outside the submitted work. Dr Mitchell reported grants from Ministry of Defence during the conduct of the study. Dr Brock reported personal fees from Invex Theraputics during the conduct of the study; and equity ownership in AstraZeneca and GlaxoSmithKline, personal fees from Eli Lilly reimbursement of costs from Merck and Roche outside the submitted work. Dr Sinclair reported fees from Invex Therapeutics as a company director with salary and stock options during the conduct of this study; and personal fees from Novartis and Allergan outside the submitted work. No other disclosures were reported.

Funding/Support: Dr Sinclair received funding from the National Institute for Health Research Clinician Scientist Fellowship (grant NIHR-CS-011-028) and the Medical Research Council, UK (grant MR/K015184/1).

Role of the Funder/Sponsor: The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Meeting Presentation: Some aspects of this work was presented at the 14th European Headache Federation Congress; virtual; July 1, 2020.

Additional Contributions: We would like to acknowledge Peter Nightgale, PhD, at the National Institute of Health Research/Wellcome Trust Clinical Research Facility, University Hospitals Birmingham NHS Foundation Trust, his advice and help during the course of the analysis. He was not compensated for his assistance.

REFERENCES

1. Duits FH, Martinez-Lage P, Paquet C, et al. Performance and complications of lumbar puncture in memory clinics: Results of the multicenter lumbar puncture feasibility study. *Alzheimers Dement*. 2016;12(2):154-163. doi:10.1016/j.jalz.2015.08.003

2. Yiangou A, Mitchell J, Markey KA, et al. Therapeutic lumbar puncture for headache in idiopathic intracranial hypertension: minimal gain, is it worth the pain? *Cephalalgia*. 2019;39(2):245-253. doi:10.1177/0333102418782192

3. Scotton WJ, Mollan SP, Walters T, et al. Characterising the patient experience of diagnostic lumbar puncture in idiopathic intracranial hypertension: a cross-sectional online survey. *BMJ Open*. 2018;8(5):e020445. doi:10.1136/bmjopen-2017-020445

4. Mitchell JL, Mollan SP, Vijay V, Sinclair AJ. Novel advances in monitoring and therapeutic approaches in idiopathic intracranial hypertension. *Curr Opin Neurol*. 2019;32(3):422-431. doi:10.1097/WCO.0000000000000690

5. Koskinen L-OD, Grayson D, Olivecrona M. The complications and the position of the Codman MicroSensor™ ICP device: an analysis of 549 patients and 650 Sensors. *Acta Neurochir (Wien)*. 2013;155(11):2141-2148. doi:10.1007/s00701-013-1856-0

6. Mollan SP, Davies B, Silver NC, et al. Idiopathic intracranial hypertension: consensus guidelines on management. *J Neurol Neurosurg Psychiatry*. 2018;89(10):1088-1100. doi:10.1136/jnnp-2017-317440

7. Lee AG, Mader TH, Gibson CR, et al. Spaceflight associated neuro-ocular syndrome (SANS) and the neuro-ophthalmologic effects of microgravity: a review and an update. *NPJ Microgravity*. 2020;6:7. doi:10.1038/s41526-020-0097-9

8. Scott CJ, Kardon RH, Lee AG, Frisén L, Wall M. Diagnosis and grading of papilledema in patients with raised intracranial pressure using optical coherence tomography vs clinical expert assessment using a clinical staging scale. *Arch Ophthalmol*. 2010;128(6):705-711. doi:10.1001/archophthalmol.2010.94

9. Frisén L. Swelling of the optic nerve head: a staging scheme. *J Neurol Neurosurg Psychiatry*. 1982;45(1):13-18. doi:10.1136/jnnp.45.1.13

10. Patel MD, Malhotra K, Shirazi Z, Moss HE. Methods for quantifying optic disc volume and peripapillary deflection volume using radial optical coherence tomography scans and association with intracranial pressure. *Front Neurol*. 2019;10:798. doi:10.3389/fneur.2019.00798

11. Auinger P, Durbin M, Feldon S, et al; OCT Sub-Study Committee for NORDIC Idiopathic Intracranial Hypertension Study Group. Baseline OCT measurements in the idiopathic intracranial hypertension treatment trial, part II: correlations and relationship to clinical features. *Invest Ophthalmol Vis Sci*. 2014;55(12):8173-8179. doi:10.1167/iovs.14-14961

12. Albrecht P, Blasberg C, Ringelstein M, et al. Optical coherence tomography for the diagnosis and monitoring of idiopathic intracranial hypertension. *J Neurol*. 2017;264(7):1370-1380. doi:10.1007/s00415-017-8532-x

13. Kaufhold F, Kadas EM, Schmidt C, et al. Optic nerve head quantification in idiopathic intracranial hypertension by spectral domain OCT. *PLoS One*. 2012;7(5):e36965. doi:10.1371/journal.pone.0036965

14. Swanson JW, Aleman TS, Xu W, et al. Evaluation of optical coherence tomography to detect elevated intracranial pressure in children. *JAMA Ophthalmol*. 2017;135(4):320-328. doi:10.1001/jamaophthalmol.2017.0025

15. Friedman DI, Liu GT, Digre KB. Revised diagnostic criteria for the pseudotumor cerebri syndrome in adults and children. *Neurology*. 2013;81(13):1159-1165. doi:10.1212/WNL.0b013e3182a55f17

16. ISRCTN Registry. IIH pressure—a new treatment for raised brain pressure in idiopathic intracranial hypertension. Published 2017. Accessed September 17, 2020. http://www.isrctn.com/ISRCTN12678718

17. Markey KA, Ottridge R, Mitchell JL, et al. Assessing the efficacy and safety of an 11β-hydroxysteroid dehydrogenase type 1 inhibitor (AZD4017) in the idiopathic intracranial hypertension drug trial, IIH:DT: clinical methods and design for a phase II randomized controlled trial. *JMIR Res Protoc*. 2017;6(9):e181. doi:10.2196/resprot.7806

18. Markey K, Mitchell J, Botfield H, et al 11β-Hydroxysteroid dehydrogenase type 1 inhibition in idiopathic intracranial hypertension: a double-blind randomized controlled trial. *Brain Communications* Published online January 2, 2020. doi:10.1093/braincomms/fcz050

19. Ottridge R, Mollan SP, Botfield H, et al. Randomised controlled trial of bariatric surgery versus a community weight loss programme for the sustained treatment of idiopathic intracranial hypertension: the Idiopathic Intracranial Hypertension Weight Trial (IIH:WT) protocol. *BMJ Open*. 2017;7(9):e017426. doi:10.1136/bmjopen-2017-017426

20. Cruz-Herranz A, Balk LJ, Oberwahrenbrock T, et al; IMSVISUAL consortium. The APOSTEL recommendations for reporting quantitative optical coherence tomography studies. *Neurology*. 2016;86(24):2303-2309. doi:10.1212/WNL.0000000000002774

21. Tewarie P, Balk L, Costello F, et al. The OSCAR-IB consensus criteria for retinal OCT quality assessment. *PLoS One*. 2012;7(4):e34823. doi:10.1371/journal.pone.0034823

22. Schippling S, Balk LJ, Costello F, et al. Quality control for retinal OCT in multiple sclerosis: validation of the OSCAR-IB criteria. *Mult Scler*. 2015;21(2):163-170. doi:10.1177/1352458514538110

23. D'Antona L, McHugh JA, Ricciardi F, et al. Association of intracranial pressure and spontaneous retinal venous pulsation. *JAMA Neurol*. 2019;76(12):1502-1505.

24. Skau M, Yri H, Sander B, Gerds TA, Milea D, Jensen R. Diagnostic value of optical coherence tomography for intracranial pressure in idiopathic intracranial hypertension. *Graefes Arch Clin Exp Ophthalmol*. 2013;251(2):567-574. doi:10.1007/s00417-012-2039-z

25. Dreesbach M, Joachimsen L, Küchlin S, et al. Optic nerve head volumetry by optical coherence tomography in papilledema related to idiopathic intracranial hypertension. *Transl Vis Sci Technol*. 2020;9(3):24. doi:10.1167/tvst.9.3.24

26. Skau M, Milea D, Sander B, Wegener M, Jensen R. OCT for optic disc evaluation in idiopathic intracranial hypertension. *Graefes Arch Clin Exp Ophthalmol*. 2011;249(5):723-730. doi:10.1007/s00417-010-1527-2

27. Wang JK, Kardon RH, Kupersmith MJ, Garvin MK. Automated quantification of volumetric optic disc swelling in papilledema using spectral-domain optical coherence tomography. *Invest Ophthalmol Vis Sci*. 2012;53(7):4069-4075. doi:10.1167/iovs.12-9438

28. Scuderi G, Fragiotta S, Scuderi L, Iodice CM, Perdicchi A. Ganglion cell complex analysis in glaucoma patients: what can it tell us? *Eye Brain*. 2020;12:33-44. doi:10.2147/EB.S226319

29. Kupersmith MJ, Garvin MK, Wang JK, Durbin M, Kardon R. Retinal ganglion cell layer thinning within one month of presentation for non-arteritic anterior ischemic optic neuropathy. *Invest Ophthalmol Vis Sci*. 2016;57(8):3588-3593. doi:10.1167/iovs.15-18736

30. Moster SJ, Moster ML, Scannell Bryan M, Sergott RC. Retinal ganglion cell and inner plexiform layer loss correlate with visual acuity loss in LHON: a longitudinal, segmentation OCT analysis. *Invest Ophthalmol Vis Sci*. 2016;57(8):3872-3883. doi:10.1167/iovs.15-17328

31. Walter SD, Ishikawa H, Galetta KM, et al. Ganglion cell loss in relation to visual disability in multiple sclerosis. *Ophthalmology*. 2012;119(6):1250-1257. doi:10.1016/j.ophtha.2011.11.032

32. Monteiro ML, Afonso CL. Macular thickness measurements with frequency domain-OCT for quantification of axonal loss in chronic papilledema from pseudotumor cerebri syndrome. *Eye (Lond)*. 2014;28(4):390-398. doi:10.1038/eye.2013.301

33. Cello KE, Keltner JL, Johnson CA, Wall M; NORDIC Idiopathic Intracranial Hypertension Study Group. Factors affecting visual field outcomes in the idiopathic intracranial hypertension treatment trial. *J Neuroophthalmol*. 2016;36(1):6-12. doi:10.1097/WNO.0000000000000327

34. Aojula A, Mollan SP, Horsburgh J, et al. Segmentation error in spectral domain optical coherence tomography measures of the retinal nerve fibre layer thickness in idiopathic intracranial hypertension. *BMC Ophthalmol*. 2018;17(1):257. doi:10.1186/s12886-017-0652-7

35. Liu X, Kale AU, Capewell N, et al. Optical coherence tomography (OCT) in unconscious and systemically unwell patients using a mobile OCT device: a pilot study. *BMJ Open*. 2019;9(11):e030882. doi:10.1136/bmjopen-2019-030882