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# Baseline OCT Measurements in the Idiopathic Intracranial Hypertension Treatment Trial, Part II: Correlations and Relationship to Clinical Features

OCT Sub-Study Committee for the NORDIC Idiopathic Intracranial Hypertension Study Group

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See the appendix for the members of the OCT Sub-Study Committee and the NORDIC Idiopathic Intracranial Hypertension Study Group.

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**Purpose.** The accepted method to evaluate and monitor papilledema, Frisén grading, uses an ordinal approach based on descriptive features. Part I showed that spectral-domain optical coherence tomography (SD-OCT) in a clinical trial setting provides reliable measurement of the effects of papilledema on the optic nerve head (ONH) and peripapillary retina, particularly if a 3-D segmentation method is used for analysis.[1] We evaluated how OCT parameters are interrelated and how they correlate with vision and other clinical features in idiopathic intracranial hypertension (IIH) patients.

**Methods.** A total of 126 subjects in the IIH Treatment Trial (IIHTT) OCT substudy had Cirrus SD-OCT optic disc and macula scans analyzed by using a 3-D segmentation algorithm to derive retinal nerve fiber layer (RNFL) thickness, total retinal thickness (TRT), retinal ganglion cell layer plus inner plexiform layer (GCL+IPL) thickness, and ONH volume. The SD-OCT parameter values were correlated with high- and low-contrast acuity, perimetric mean deviation, Frisén grading, and IIH features.

**Results.** At study entry, the average RNFL thickness, TRT, and ONH volume showed significant strong correlations ($r \geq 0.90$) with each other. The same OCT parameters showed a strong ($r > 0.76$) correlation with Frisén grade and a mild ($r > 0.24$), but significant, correlation with lumbar puncture opening pressure. For all eyes at baseline, neither visual acuity (high or low contrast) nor mean deviation correlated with any OCT measure of swelling or GCL+IPL thickness.

**Conclusions.** In newly diagnosed IIH, OCT demonstrated alterations of the peripapillary retina and ONH correlate with Frisén grading of papilledema. At presentation, OCT measures of papilledema, in patients with newly diagnosed IIH and mild vision loss, do not correlate with clinical features or visual dysfunction. (ClinicalTrials.gov number, NCT01003639.)

Keywords: papilledema, intracranial hypertension, OCT, lumbar puncture

In the preceding report,[1] we have shown that spectral-domain optical coherence tomography (SD-OCT) can provide high-quality data in patients with papilledema due to idiopathic intracranial hypertension (IIH), from multiple clinical sites working with an experienced OCT reading center. Optical coherence tomography imaging reliably and reproducibly demonstrates alterations in the optic nerve head (ONH) and retinal layers in IIH, which includes measurement of the average peripapillary retina nerve fiber layer (RNFL) thickness, average total peripapillary retinal thickness (TRT), ONH volume, and the ganglion cell plus inner plexiform layer thickness (GCL+IPL) in the macular region. Moreover, interocular comparisons for all OCT parameters reflecting swelling of the ONH or peripapillary retina were significant and highly correlated. As expected, 90% of eyes (220/244 with Zeiss algorithm–derived RNFL thickness values) of the enrolled subjects exhibited significant (>95th percentile) thickening of the RNFL. Only 7% of the study eyes showed significant thinning (<fifth percentile) of the GCL+IPL layer at presentation.

For IIH Treatment Trial (IIHTT) eyes, the proprietary algorithm used in commercial OCT device displayed noteworthy failure rates in the measurement of average RNFL thickness (10%), total retinal thickness (16%), and ganglion cell layer thickness (20%). The 3-D segmentation algorithm from the University of Iowa engineering group[2] was less prone to failure, with rates of 2.4%, 2.4%, and 0.8%, respectively for the same OCT parameters. Prior studies of eyes with significant ONH swelling have shown that 2-D segmentation analysis failures are common when using the proprietary OCT algorithms for measuring RNFL thickness with SD-OCT (Mandel G, et al. *IOVS* 2010;51:ARVO E-Abstract 555), TRT with time-domain OCT,[3] and GCL+IPL thickness determinations in the setting of ONH swelling (Kupersmith MJ, et al. *IOVS* 2013;54:ARVO E-Abstract 3233). Given the reliability and accuracy of the 3-D segmentation algorithm, we used OCT results derived from 3-D segmentation for correlation analysis.

Prior reports (see Discussion) suggest that there are a number of clinical features in IIH that might correlate with the degree of papilledema and the opening cerebrospinal fluid (CSF) pressure measured by lumbar puncture (LP). Because the IIHTT specifically selected newly diagnosed patients with mild vision loss, we hypothesized that structural loss in the retina or ONH should be uncommon at baseline. The purpose of this report (Part II) was to evaluate the relationship between OCT

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**Table 1.** Description of the Screening/Baseline Demographics for Subjects in the OCT Substudy

| Label | N | Mean | Std Dev | Minimum | Maximum |
|---|---|---|---|---|---|
| Age, y | 126 | 28.9 | 7.5 | 18.0 | 52.0 |
| Calculated BMI, kg/m$^2$ | 125 | 40.1 | 8.3 | 26.3 | 71.2 |
| CSF pressure, mm $H_2O$ | 125 | 340.5 | 82.9 | 220.0 | 560.0 |
| Time from LP to OCT, d | 125 | 4.6 | 9.3 | −13.0* | 55.0 |
| Amount of weight gain, lb | 73 | 22.3 | 16.3 | 4.0 | 100.0 |
| Visual acuity, letters correct | 126 | 56.0 | 5.6 | 36.0 | 70.0 |
| Low-contrast visual acuity, letters correct | 126 | 27.1 | 11.1 | 0.0 | 66.0 |
| PMD in the study eyes, dB | 126 | −3.5 | 1.0 | −6.4† | −2.0 |

Description of the screening/baseline demographics for subjects in the OCT substudy with visual acuity, low-contrast visual acuity, and PMD shown for study eyes. Std Dev, standard deviation.

* Twenty-six subjects had OCT performed before the LP (a negative number of days means that the OCT was performed a number of days before OCT).

† Minimum PMD is the most severe visual field loss.

parameters and to correlate these parameters with Frisén grading of papilledema, visual performance, and other clinical features of IIH.

## Methods

We used the baseline data collected in the IIHTT OCT substudy reported in Part I[1] for 126 IIHTT subjects, all of whom met study entry criteria.[4] The study eye (126/252), defined as having the worse mean deviation on automated visual field testing of the two eyes, was used to explore potential relationships among OCT parameters and clinical features of IIH. The OCT structural parameters studied by using 3-D segmentation were average thickness of the RNFL, TRT, and average macula GCL+IPL, and ONH volume. In addition, the ONH height, manually measured by the OCT Reading Center using the high-density horizontal raster scans through the ONH, was determined. The GCL+IPL thickness values were also analyzed as a percentile of the Carl Zeiss Meditec, Inc. (Zeiss, Dublin, CA, USA)–provided age-matched controls. For this process we used the 3-D segmentation algorithm to analyze and segment the Zeiss control eye raw scans to provide GCL+IPL percentile scores for comparison. For study eyes, we defined GCL+IPL as thinned if the values fell below the fifth percentile of the segmentation derived by 3-D for the Zeiss control eyes.

The IIH clinical characteristics, collected under the IIHTT protocol, were compared to the OCT findings. Frisén grade of papilledema was determined from digital photographs evaluated by the Photographic Reading Center and also by clinical examination (not by photo review at the site) performed by the principle investigator at each site. Specific IIH clinical features that were studied included amount of self-reported recent weight gain, body mass index (BMI), CSF opening pressure in mm $H_2O$, and number of days the OCT was performed before or after LP. The baseline measures were assessed by certified technicians, using study-specific procedures to measure the best corrected visual acuity (reported as number of letters seen) for high (100%) and low (2.5%) contrast charts, and perimetric mean deviation (PMD) on automated threshold visual field testing.[1,4]

Descriptive statistics (e.g., quartiles, means, and standard deviations) were used to summarize screening and baseline demographic and clinical characteristics of the 126 subjects in the OCT substudy. The degree of papilledema in these subjects was determined by frequency distributions of Frisén grade based on examination and digital photographs. Pearson correlation coefficients were used to assess the relationships among the OCT measures and between the OCT measures and the clinical characteristics of the sample, including tests of vision function and IIH clinical features. The *t*-tests were used to compare subjects with thinned GCL+IPL (<fifth percentile of controls) to subjects $\geq$ fifth percentile of controls with regard to IIH vision-testing measures. Spearman correlation coefficients and Wilcoxon-Mann-Whitney tests were used to investigate these associations with Frisén grading. The *t*-tests were used to compare mean OCT measures between subjects with GCL+IPL > 95th percentile of controls to subjects $\leq$ 95th percentile of controls and between subjects who had the OCT performed before the LP versus after the LP. $P$ values $< 0.05$ were considered statistically significant.

## Results

Table 1 summarizes the descriptive statistics of the demographics and clinical data of the study subjects, which we used to correlate with the SD-OCT parameters. Subject age, PMD, and days between LP and OCT performance were relatively narrow, given the IIHTT subject entry criteria and testing protocol (Table 1). Except for rare exceptions made by the IIHTT study director, study entry criteria required the opening pressure be at least 25 cm $H_2O$, so the elevation of CSF opening pressure in almost all subjects was expected, but the range of pressures was wide. The distribution for low-contrast visual acuity was larger than for high-contrast visual acuity. Most eyes had mild to moderate papilledema, Frisén grade 2 to 4, with grading scored from photos being slightly worse (higher grades) than those scored at the sites by ophthalmoscopy (Fig. 1).

The ONH volume, which should reflect swelling of the optic disc region, linearly correlated with the single ONH height determination made from high-density raster scans, and peripapillary RNFL and TRT. All OCT parameters reflecting swelling of the ONH and peripapillary retina were strongly and significantly correlated (Fig. 2), but not with the GCL+IPL thickness. Frisén grades, as determined by evaluation on ophthalmoscopy and by photos, significantly correlated with OCT measures of swelling in the ONH and peripapillary retina (Table 2), but not with GCL+IPL values.

The OCT was performed before the LP in 26 subjects and after the LP in 99 subjects. Comparing these two groups, there was no significant difference for ONH volume (mean, 16.9 mm$^3$ pre versus 16.4 mm$^3$ post; $P = 0.59$), RNFL thickness (mean, 285 μm pre versus 272 μm post; $P = 0.72$), or TRT (mean, 550 μm pre versus 539 μm post; $P = 0.82$). Nine study eyes (7%) with 3-D segmentation–derived GCL+IPL thickness values that were less than the Zeiss control fifth percentile had significantly worse high-contrast visual acuity ($P = 0.01$) than eyes with

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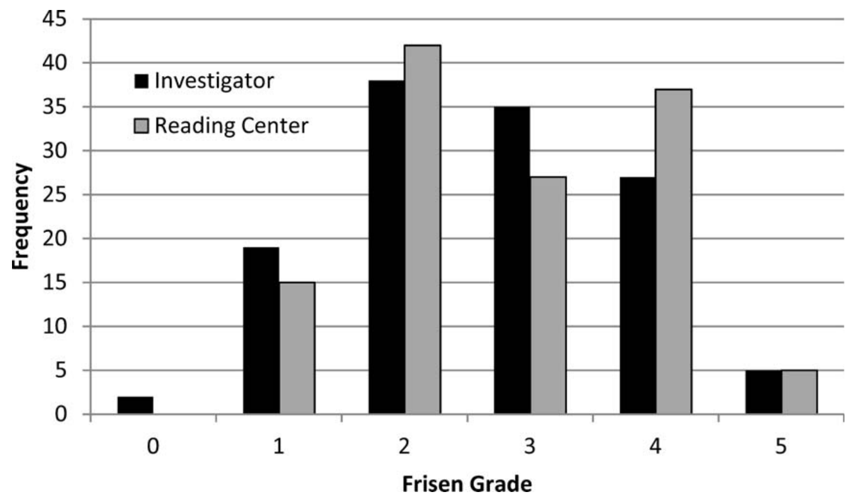


**Figure 1.** There was general agreement between the reading center and the clinical site investigators in the staging of papilledema, using the Frisén scale. The most frequent grades of papilledema were 2 to 4.

GCL+IPL thickness equal to or greater than the control fifth percentile. However, there was no significant difference in low-contrast visual acuity and visual field mean deviation (Table 3). Frisén grades were not significantly different between the group of eyes showing an abnormally thinned GCL+IPL, compared to those that showed normal thickness.

Ten study eyes (8%) had GCL+IPL thickness greater than the 95th percentile for Zeiss controls. All 10 eyes had greater RNFL

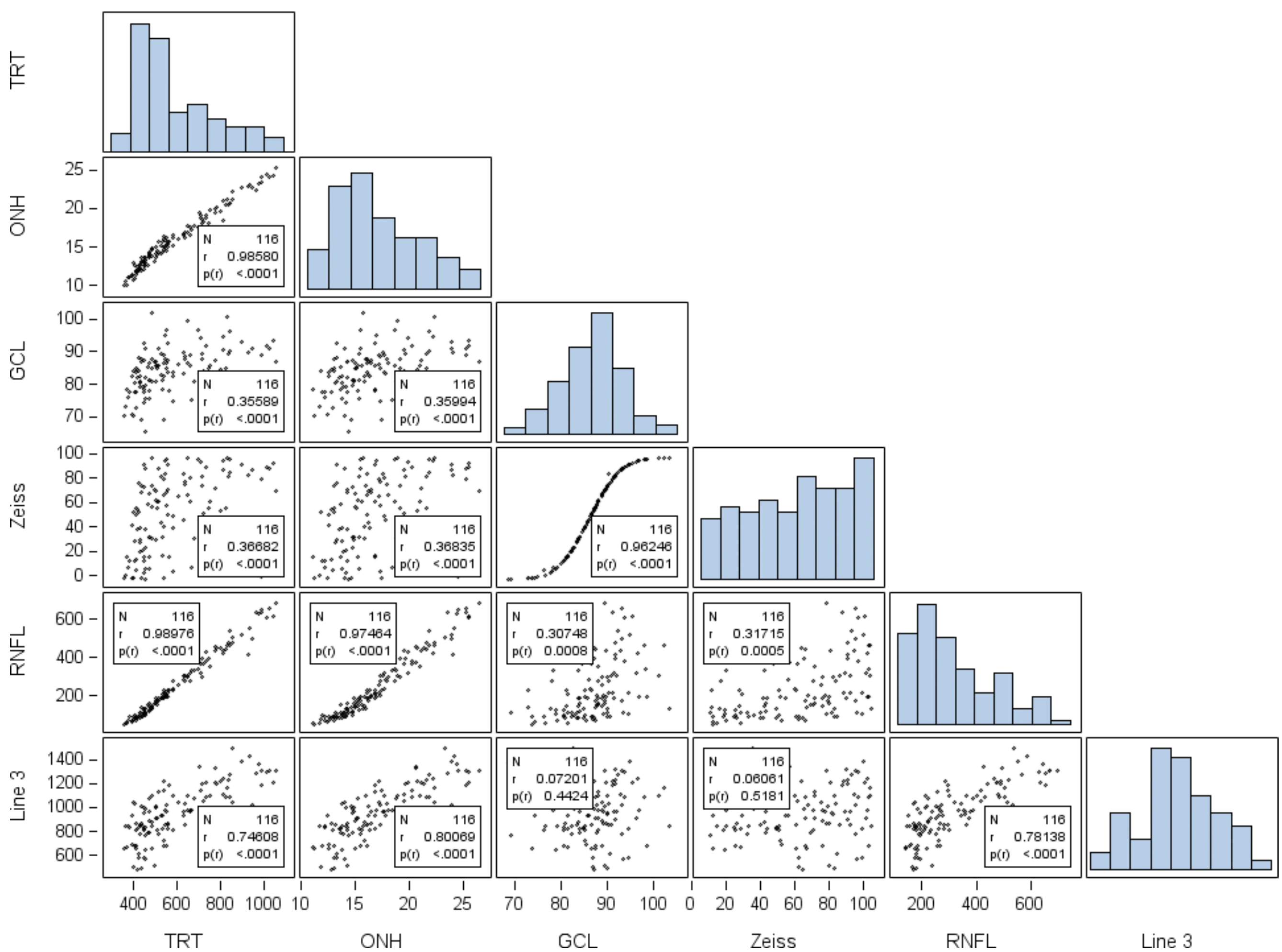


**Figure 2.** *Scatter plots* for OCT measures in study eyes, using Pearson correlations. *Top* of figure shows frequency distribution histogram for all parameters. GCL, GCL+IPL average thickness for the macular region; Line 3, ONH height measured by using Line 3 of the SD raster lines; N, number of study eyes with data for each OCT measure; ONH, total optic nerve head volume; p(r) = *P* value; Zeiss, percentile Zeiss controls.

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**Table 2.** Significant Correlations for OCT Parameter Values and Clinical Features

| | Correlation With RNFL | Correlation With TRT | Correlation With ONH Volume *r* Value, *P* Value | Correlation With ONH Height by Raster Line 3 |
|---|---|---|---|---|
| Frisén grade by photos | 0.77, 0.0001 | 0.76, 0.0001 | 0.80, 0.0001 | 0.76, 0.0001 |
| Frisén grade by investigators | 0.71, 0.0001 | 0.67, 0.0001 | 0.69, 0.0001 | 0.66, 0.0001 |
| CSF opening pressure | 0.22, 0.02 | 0.23, 0.01 | 0.23, 0.01 | NS |

Clinical feature Spearman correlations with OCT measurements. NS, weak not significant correlation.

thickness, TRT, and ONH volume than for eyes with GCL+IPL less than the 95th percentile of controls (RNFL mean = 365 ± 148 µm versus 262 ± 163 µm; $P = 0.06$; TRT mean = 676 ± 190 µm versus 524 ± 202 µm, $P = 0.02$; ONH volume mean = 19.2 ± 3.2 mm$^3$ versus 16.2 ± 3.7 mm$^3$; $P = 0.02$).

There was no significant correlation for any OCT parameter when compared with the high- or low-contrast visual acuity or PMD when all study eyes were analyzed together (data not shown). None of the clinical features of IIH (data not shown) correlated with the OCT parameters except for the CSF opening pressure. The correlations between CSF opening pressure and ONH volume, TRT, and RNFL thickness were minor but significant (Table 2).

## Discussion

All four OCT measures of ONH and peripapillary retina swelling, ONH volume, ONH height, peripapillary RNFL thickness, and peripapillary TRT, were strongly correlated. The SD-OCT imaging provides continuous measures of structural changes due to ONH swelling associated with papilledema. Before treatment, eyes with mild vision loss had

**Table 3.** Description (Quartiles, Limits) of Vision Testing and Frisén Grade of Study Eyes Divided by if GCL+IPL < Fifth Percentile or ≥Fifth Percentile of Zeiss Controls (Matched for Age)

| | N | Mean | Std Dev | Minimum | Maximum |
|---|---|---|---|---|---|
| High-contrast visual acuity number correct | | | | | |
| GCL+IPL < 5% | 9 | 51.4 | 6.9 | 36.0 | 58.0 |
| GCL+IPL ≥ 5% | 115 | 56.4 | 5.4 | 36.0 | 70.0 |
| $P = 0.01$ | | | | | |
| Low-contrast visual acuity number correct | | | | | |
| GCL+IPL < 5% | 9 | 21.9 | 13.1 | 2.0 | 41.0 |
| GCL+IPL ≥ 5% | 115 | 27.5 | 11.0 | 0.0 | 66.0 |
| $P = 0.15$ | | | | | |
| PMD, dB | | | | | |
| GCL+IPL < 5% | 9 | −3.1 | 0.7 | −4.0 | −2.2 |
| GCL+IPL ≥ 5% | 115 | −3.5 | 1.1 | −6.4 | −1.9 |
| $P = 0.23$ | | | | | |
| Frisén grade by site examination | | | | | |
| GCL+IPL < 5% | 9 | 2.6 | 0.9 | 1.0 | 4.0 |
| GCL+IPL ≥ 5% | 115 | 2.6 | 1.2 | 0.0 | 5.0 |
| $P = 0.85$ | | | | | |
| Frisén grade by photos | | | | | |
| GCL+IPL < 5% | 9 | −3.1 | 0.7 | −4.0 | −2.2 |
| GCL+IPL ≥ 5% | 115 | −3.5 | 1.1 | −6.4 | −1.9 |
| $P = 0.71$ | | | | | |

Description (quartiles, limits) of vision testing and Frisén grade of study eyes divided by if GCL+IPL < fifth percentile or ≥fifth percentile of Zeiss controls (matched for age). Std Dev, standard deviation.

average peripapillary RFNL thickness, peripapillary TRT, and ONH volume, calculated using 3-D segmentation, that showed major significant correlations with the Frisén grade reported by the site investigators and by fundus photo analysis. The modified Frisén staging system used in the IIHTT is an ordinal scale, based in part on the degree and the location of axonal distension and opacification. Early on this loss of translucency develops along the vertical poles and nasal margins of the optic disc, producing a "C"-shaped whitish halo at the disc margin (grade I) that spreads temporally (grade II). Continued thickening of the RNFL progressively obscures some of the blood vessels at the disc margin (grade III), then obscures vessels on the optic disc itself (grade IV), and eventually obscures all of the vessels on the disc (grade V). At study entry, the current study showed that the Frisén grade, as reported both by the site investigators and by fundus photo analysis, significantly correlated with the average peripapillary RFNL thickness ($r = 0.77$), the peripapillary TRT ($r = 0.76$), and the ONH volume ($r = 0.80$). This is in agreement with a smaller study using time domain, by Scott et al.,[3] which has shown a significant correlation for RNFL ($r = 0.85$) and for TRT ($r = 0.87$), with Frisén grades of photographs in 36 eyes of 36 IIH patients. None of the SD-OCT parameters appeared to be superior for correlating with the papilledema grading.

The TRT measurement was more reliable than the proprietary algorithm for RNFL calculation for these time-domain results. However, the IIHTT 3-D segmentation–derived data from SD-OCT had only a 3% failure rate for the average RNFL or TRT or ONH volume. Additionally, we did not find a broader range of RNFL thickness, TRT, or ONH volume in eyes with worse Frisén grades as in the study by Scott et al.[3]; however, their entry criteria are different and include patients with a wider range of visual field loss. In another study that used SD-OCT, the RNFL thickness and TRT correlate with papilledema severity, but the study only evaluates 22 eyes with intracranial hypertension, 16 of which are due to IIH.[5] In addition, this study[5] reports that the TRT correlates better than RNFL thickness in the 18 eyes with a mild papilledema grade.

There was a small but statistically significant correlation between CSF opening pressure with the Frisén grade and all four OCT parameters of papilledema-related swelling, ONH volume and height, TRT, and RNFL thickness. The amount of ONH volume and height had a modest correlation with CSF opening pressure. This result differed from the findings of Heckman et al.,[6] who have used optic disc height and found a much stronger correlation ($r$ value approximately 0.60) with CSF opening pressure. The difference may be explained by a difference in the timing of the optical scanning relative to the LP. In the study by Heckman et al.,[6] 17 patients had the LP performed just before imaging with laser scanning tomography. The timing of the OCT relative to the LP may be important. It is well known that immediately following an LP, there may be temporary improvement of IIH symptoms and in some cases, a postspinal tap headache suggests the procedure can transiently lower the CSF pressure. Furthermore, there is evidence that the shape deformation of Bruch's membrane and the RNFL

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thickness can decrease after LP.[7] The subjects in the IIHTT had SD-OCTs performed on average 4.6 days after the LP and only 20% had SD-OCT before the LP. Further, we did not have immediate pre- and post-LP OCT data collected for subjects. Nevertheless, the IIHTT data showed no correlation between the number of days between LP and SD-OCT imaging and the OCT parameters or the Frisén grade. Additionally, subjects with SD-OCTs performed before LP did not have greater swelling by OCT or Frisén grades. In a more recent report relating increased macular region TRT to RNFL thickening by time-domain OCT, the severity of papilledema correlates with the severity of elevated intracranial pressure but the LPs used to provide the pressures were typically performed months before the OCT imaging and the authors do not detail the therapies of the subjects at the time the OCT was performed.[8] In addition, owing to limitations of OCT methodology in the latter study, the amount of RNFL swelling could not be calculated in some subjects. Finally, the IIHTT OCT substudy was not specifically designed to examine the short-term effects of an LP on OCT measures of papilledema, and the wide range of retinal thickness and ONH volume measurements (Part I, Table 2[1]) might mask all but extreme relationships.

The manual measurement of ONH height, using the high-density raster scans, appears equally effective in showing the effects of intracranial hypertension, but has more repeated measurement variability (see Part I[1]). This parameter can also be used to determine the width of the Bruch's membrane opening and a manually determined volume measurement of the swelling of the optic nerve in the neural canal.

Given the limits of IIHTT study eligibility, no subjects had major visual acuity or visual field deficits; thus, we hypothesized that few if any subjects would have significant nerve loss at the time of enrollment. However, it is possible that the amount of RNFL edema and axonal swelling limited our ability to show early RNFL axonal thinning or loss. At presentation, no measure of vision performance, high- or low-contrast acuity or PMD, correlated with any OCT measure of peripapillary retinal or optic nerve head swelling. This differs from prior reports suggesting the extent of papilledema or TRT or RNFL swelling correlates with the amount of visual deficits. For example, in 20 newly diagnosed patients with IIH (including cases that had symptoms for longer than 5 years), vision function is said to correlate with time-domain–derived RNFL and TRT thickness.[8] Rebolleda and Munoz-Negrete[9] describe a −0.45 correlation coefficient ($P = 0.002$) with PMD for the initial evaluations in 44 eyes of 22 IIH patients, including eyes with moderate visual field loss. None of the prior reports include a cohort using similar entry criteria as in the IIHTT, which included only newly diagnosed patients with IIH and with vision loss that was mild. Thus, it is possible that the difference in results may be explained by the differences in disease severity or duration of the patients studied. Since all IIHTT study eyes had abnormal (albeit mild, PMD = −2 dB to −7 dB) mean deviation in the study eye, it is not unexpected that low-contrast visual acuity (median = 28 letters) was frequently reduced in these eyes. This level of reduced low-contrast vision is similar to reported results in patients with multiple sclerosis without a history of optic neuritis (mean, 26 ± 11) and clearly worse than controls (34 ± 8), with mean age of 33 ± 15 years, which is similar to the age of IIHTT subjects.[10]

The 3-D segmentation algorithm–derived SD-OCT GCL+IPL thickness was in the normal range in 93% of IIHTT study eyes, suggesting that permanent injury to the macula GCL+IPL at presentation is uncommon in patients with newly diagnosed IIH and mild visual field loss. Peripheral field loss might have been associated with RNFL thinning and retina ganglion cells outside the macular area, but the concomitant RNFL swelling prevented assessing any loss or thinning, and the GCL+IPL is too thin outside of the macula to reliably evaluate. The GCL+IPL thinning (defined as <fifth percentile of age-matched controls) via 3-D segmentation was found at baseline in only nine eyes (7%). These nine eyes had mild but significant reduced high-contrast visual acuity and a trend of worse low-contrast visual acuity and mean deviation than eyes without GCL+IPL thinning. However, when all study eyes were considered, no vision test correlated with the average thickness of the GCL+IPL. This is not surprising given the wide range of normal GCL+IPL thickness and the small number of cases with thinning. It remains to be determined whether GCL thinning at baseline is a risk factor for an outcome with poorer vision or increased RNFL thinning over time.

The GCL+IPL thickness appears to be mildly correlated with the swelling of the ONH, retina, and RNFL. A GCL+IPL thickness greater than the 95th percentile of Zeiss controls occurred in 8% of eyes and was associated with thicker ONH volume, RNFL, and TRT. Both results suggest that the axonal stasis associated with papilledema can affect both axons and soma of retinal ganglion cells in the macula. If this does occur, then early thinning of the GCL+IPL-associated neuron loss in IIH may be more difficult to detect. These findings are similar to, but considerably less than, what occurs when peripapillary RNFL swelling prevents early detection of axonal loss associated with nonarteritic anterior ischemic optic neuropathy (NAION) or optic neuritis. Thickening of the GCL+IPL is not typically seen at presentation of optic neuritis or NAION (Kupersmith MJ, et al. *IOVS* 2013;54:ARVO E-Abstract 3233), suggesting the acute onset of these two causes of optic neuropathy is different from that measured in IIH, which may have a different, gradual onset and chronicity at presentation.

The SD-OCT parameters reflecting swelling due to papilledema, RNFL thickness, TRT, and ONH volume and height were strongly correlated with the Frisén grade of papilledema at baseline in this cohort of eyes with mild vision loss due to IIH. The ONH volume correlated best with the reading center grading of photos, which is not surprising, since grading from photos may be more accurate and reproducible than from clinical examination with ophthalmoscopy. Therefore, ONH volume and the Frisén grade both reflect the swelling of the optic disc head. We do not know whether the findings of this study can be extrapolated to patients with chronic papilledema or to eyes with moderate or severe vision loss. The absence of clinical correlations, particularly visual performance deficits, with the SD-OCT findings in this group of patients with newly diagnosed IIH and mild visual loss may or may not be seen in patients with worse vision at presentation. Additionally, it is not yet known whether all of the OCT measures will change in parallel and correlate with Frisén grade as the disease state improves or worsens. The Frisén grade is a complex ordinal measurement based on a number of visual observed features, which includes, but is not limited to, swelling of the optic disc and peripapillary retina. A previous study using lower-resolution OCT imaging has shown that RNFL thickness can be used to monitor changes over time and in response to therapy in a case series of 20 patients with IIH.[11,12] We anticipate that analysis of the IIHTT subjects over time will demonstrate which, if any, SD-OCT parameter (1) will correlate with visual outcome, such as high- and low-contrast visual acuity and visual field sensitivity (PMD); (2) will improve owing to therapy or reflect IIH worsening; and (3) will appear superior to Frisén grading for monitoring papilledema.

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## Appendix

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