Multidisciplinary Ophthalmic Imaging

Relationship Between Optic Nerve Protrusion Measured by OCT and MRI and Papilledema Severity

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PURPOSE. To develop measures of optic nerve protrusion length (NPL) from optical coherence tomography (OCT) and magnetic resonance imaging (MRI) and compare these measures with papilledema severity in idiopathic intracranial hypertension (IIH).

METHODS. Optical coherence tomography and MRI scans were obtained from 11 newly diagnosed untreated IIH patients (30 ± 10 years; body mass index [BMI] 36 ± 4 kg/m²). Optic nerve protrusion length was measured for each eye using OCT and MRI independently. The relationship between the NPL measures and their association with the Frisen scale for papilledema severity were assessed. Two different OCT-based measures of NPL were derived to assess the influence of the retinal thickness on the association with papilledema severity. Additional OCT scans from 11 healthy subjects (38 ± 7 years) were analyzed to establish reliability of the NPL measurement.

RESULTS. Optical coherence tomography and MRI measurements of NPL were significantly linearly correlated (R = 0.79, P < 0.0001). Measurements of NPL from OCT and MRI were significantly associated with Frisen papilledema grade (P < 0.0001). Mean OCT measurement of NPL in the papilledema cohort was significantly larger than in the healthy cohort (0.62 ± 0.24 vs. 0.09 ± 0.03 mm, P < 0.0001).

CONCLUSIONS. Significant linear correlation between OCT and MRI measurements of NPL supports the reliability of the OCT-based measurements of NPL in papilledema. Significant association between the papilledema grade and OCT and MRI-based measurements of NPL highlights the potential of NPL as an objective and more sensitive marker of papilledema severity than the Frisen scale.

Keywords: papilledema, optic nerve protrusion, MRI, optical coherence tomography

Papilledema is swelling of the optic nerve head due to elevated intracranial pressure (ICP). This condition is associated with several etiologies, including idiopathic intracranial hypertension (IIH),1–3 sinus venous thrombosis,1,2,4–5 intracranial inflammation,1,2 intracranial mass,6,7 and subarachnoid hemorrhage.1,2 Papilledema has also been documented in astronauts during and after prolonged space flight.8,9 Studies suggest elevated ICP causes papilledema through mechanical or ischemic pathways leading to axoplasmic stasis and subsequent death of the retinal ganglion cell fibers.10,11 While the severity of papilledema has not been correlated with the degree of visual impairment, high grades of papilledema carry increased risk of visual impairment, including permanent vision loss if not treated promptly.11–13 Papilledema is evaluated clinically by fundoscopy and visual inspection of the optic nerve head. Papilledema severity is assessed based on the appearance of disc margin, height, and vascular visibility. The Frisen scale has been developed to standardize papilledema grading, but the clinical assessment of papilledema severity remains subjective and often varies among observers.14,15 Magnetic resonance imaging (MRI) signs associated with papilledema include posterior flattening of the globe, protrusion of the optic nerve, widening of the optic nerve sheath, tortuosity of the optic nerve,16–18 and presence of optic nerve head hyperintensity on diffusion-weighted imaging.19 Among these signs, MRI-derived quantitative measures of optic nerve protrusion (NP) and globe flattening (GF) were compared with papilledema grade in obese female IIH patients.20 Nerve protrusion showed a stronger correlation with papilledema grade compared with globe flattening. Therefore, NP may have diagnostic value as an objective indicator of papilledema severity.

Optical coherence tomography (OCT) is more accessible than MRI and more commonly used to image the ocular region of the optic nerve head mainly for assessing the retinal nerve fiber layer (RNFL). While OCT can be associated with geometrical distortion, it produces high-resolution cross-sectional images of the posterior globe with fast scan times. Consequently, OCT has been used to study pathological changes in papilledema and the relation of these changes to papilledema severity, demonstrating its potential as a more accurate measure of severity than an ordinal measure such as the Frisen scale.17–22 Optical coherence tomography studies have shown increased peripapillary RNFL and total retinal (TR) thickness in IIH11 and craniopetrosis-associated21 papilledema, increased peripapillary RNFL and TR volume in papilledema.
ma of unspecified etiologies,\textsuperscript{22,25} and inward deformation of the peripapillary retinal pigment epithelium (RPE) and Bruch’s membrane in IIH-associated papilledema.\textsuperscript{3} Retinal nerve fiber layer thickness, TR thickness,\textsuperscript{25} and TR volume\textsuperscript{22} were found to be associated with papilledema grade but difficult to quantify as segmentation of the retinal fiber layers often failed, especially in cases of severe papilledema. This study explored the relationship between measurements of nerve protrusion length (NPL) derived independently from MRI and OCT scans of the same IIH patient cohort and determines their relationships to papilledema grade. Agreement between measurements from both modalities would confirm the validity of the proposed OCT-based measurement of NPL.

**Materials and Methods**

**Study Participants**

The study was performed in adherence with the tenets of the Declaration of Helsinki. All study participants provided written informed consent approved by the institutional review board. Optical coherence tomography and MRI data of 22 globes were obtained from a cohort of 11 overweight women (30 \pm 10 years; range, 17–44 years; mean body mass index, 36 \pm 4 kg/m\textsuperscript{2}; range, 29–43 kg/m\textsuperscript{2}) with a confirmed newly-diagnosed, untreated IIH as per the modified Dandy criteria\textsuperscript{26} and the updated IIH criteria proposed more recently.\textsuperscript{27,28} Optical coherence tomography data for an additional 22 globes from 11 healthy women (38 \pm 7 years) were also obtained.

Detailed neurologic symptoms and ophthalmologic assessments were obtained by an experienced neuro-ophthalmologist. Papilledema severity was classified by fundoscopic examination using the Frisen scale, an ordinal scale ranging from 0 (normal optic disc) to 5 (severe papilledema) based on the appearance of the disk margin and the overlying retinal blood vessels.\textsuperscript{29} All of the IIH subjects had bilateral papilledema (median grade, 2; range, 1–4).

**OCT Scan Protocol and Quantitation of Nerve Protrusion Length**

Optical coherence tomography scans were acquired using a Cirrus High Density SD-OCT (Carl Zeiss Meditec, Dublin, CA, USA), producing a \(2 \times 6 \times 6\)-mm image cube (200 slices) around the optic nerve head. Automated quantitation of NPL from OCT images was performed in four steps: (1) identification of the inner limiting membrane (ILM), (2) generation of a three-dimensional (3D) surface, (3) smoothing, and (4) determination of baseline level. First, the depth of the ILM was detected from individual b-scans using thresholding. The identified anterior boundary from each b-scan was overlaid axially to form a 3D representation of the ILM. The resulting surface was smoothed using a median filter to remove speckle noise. Finally, a reference baseline level needed for determining the length of the protrusion was identified. Two different reference levels were tested. The first uses a low order polynomial curve fit of the ILM excluding the region of nerve protrusion (R1) and the second uses the RPE level (R2), resulting in two separate calculations of NPL, NPL-OCT\textsubscript{R1}, and NPL-OCT\textsubscript{R2}, respectively. In each case, NPL was then defined as the maximum height of the 3D surface relative to the reference level.

**MRI Scan Protocol and Quantitation of Nerve Protrusion Length**

Magnetic resonance imaging was performed only in IIH patients using a 1.5T scanner (Symphony; Siemens, Erlangen, Germany). Quantitative assessment of the globes was obtained from a 3D CISS sequence with an isotropic resolution of 0.6 mm and the following imaging parameters: TR, 6.35 ms, TE, 2.82 ms, flip angle, 47°, bandwidth, 560 Hz/pixel, and a scan time of approximately 3 minutes.

Nerve protrusion length measurement by MRI is based on a previously described MRI measurement of globe deformation that converts the 3D geometry of the globe’s posterior wall into a 2D map of the distances from the center of the globe to the head of the optic nerve and the surrounding region.\textsuperscript{20} The MRI-based measurement of NPL (NPL-MRI) was defined as the difference in the mean distance between a circular region of interest (ROI) centered on the optic nerve head and an annular ROI covering a peripheral section of the globe posterior hemisphere.

**Statistical Methods**

Associations between the OCT measurements of NPL derived using the two different references and MRI-derived NPL were tested by calculation of Pearson correlation coefficients. In addition, Bland-Altman plots and a paired \(t\) test were done to assess the level of agreement between the two modalities. Associations between NPL measurements from OCT and MRI and papilledema grade, an ordinal parameter, were tested using Spearman rank correlation, which best estimates statistical dependence between two monotonically related variables that may not be linearly related. Image and statistical analysis of both OCT and MRI data were implemented by use of Matlab (MathWorks, Natick, MA, USA).

**Results**

An example of an OCT scan line in a region that includes the optic disk with the automatically identified ILM (blue) and RPE (red) layers is shown in Figure 1. The OCT and corresponding MRI-derived geometries of the posterior globe region that includes the optic nerve head from the right and left eye of an IIH patient with papilledema grades of 4 in both eyes are shown in Figure 2. The presence of optic nerve protrusion can be clearly visualized in the surface reconstruction from both modalities.

Box-and-whisker plots of the OCT-based NPL measurements derived using the ILM as reference (R1) for the IIH patients and healthy subjects are shown in Figure 3. Average NPL-OCT\textsubscript{R1} from the IIH patients were significantly longer than the control cohorts with NPL values of 0.62 \pm 0.24 vs. 0.09 \pm 0.03 mm, \(P < 0.0001\), respectively. The OCT-based NPL values derived
using the RPE layer as a reference were very strongly correlated with those obtained using the ILM as a reference with a slope of 1.09 and $R$ value of 0.98. A Bland-Altman plot of the differences between the two OCT measurements of NPL is shown in Figure 4. As expected, NPL-OCT$_{R2}$ was longer by an average value of 0.38 mm due to the use of a deeper baseline reference for NPL-OCT$_{R2}$. The 95% confidence interval was ±0.11 mm.

The NPL measurements from the two modalities are significantly linearly correlated, both with $R$ values of 0.79 ($P < 0.0001$). Bland-Altman plots of the MRI- and OCT-derived NPL values using the two different references from the IIH patients are shown in Figures 5A and 5B, respectively. The plot of the MRI-OCT$_{R1}$ NPL measurements revealed a mean bias of 0.44 ± 0.24 mm (longer MRI-based NPL measures), while measurements of NPL with the RPE layer as a reference (NPL-OCT$_{R2}$) were more similar to the MRI measurements with a smaller bias of only 0.05 ± 0.24 mm with corresponding $P$ values of $P$ less than 0.0001, and $P$ equal to 0.3, respectively.

The monotonic relationships between the MRI- and OCT-derived NPL measures and papilledema severity assessed by Frisen grades are shown in Figure 6. Both the MRI- and OCT-derived measures were significantly associated with Frisen grades with Spearman correlation coefficients of $\rho$ equal to 0.76, $P$ less than 0.0001, and $\rho$ equal to 0.66, $P$ less than 0.0001, respectively. The Spearman correlation coefficients for the two OCT-based NPL measurements were similar.

**DISCUSSION**

Recently reported quantitative imaging of the globe distortion in IIH by MRI$^{20}$ provided important insight into the association between papilledema severity and ocular structural changes. A relative measure of nerve protrusion demonstrated the strongest association with papilledema severity determined using the Frisen scale.$^{20}$ This association supports the view of a mechanical origin of papilledema, and thereby the importance of measuring the degree of NP to assess progression of papilledema. The current study demonstrates that nerve protrusion length can be measured by MRI and OCT with a high degree of reliability and consistency. The study demonstrates a strong correlation between the MRI and OCT measures of NPL and further confirms its association with papilledema severity.
The current standard for determining papilledema severity is the Frisen scale, a subjective ordinal rating system. Therefore, it lacks the sensitivity of a continuous objective measure. The results of this study suggest that NPL is a potential candidate for complementing the Frisen scale with a more sensitive marker of papilledema severity than the Frisen scale alone.

Optical coherence tomography–derived measurements of NPL were shown to be precise and reliable with very reproducible results as indicated by the small variability found in NPL measurements in the healthy control cohort, the large significant difference between patients with papilledema and the healthy controls, and the association with papilledema severity. The reliability of NPL quantitation by OCT is further inferred by the consistency between the NPL values obtained using the two different and independent estimations of baseline references.

Optical coherence tomography scanning of the posterior globe is performed at an angle to the optical axis but oriented parallel to the optical axis during image reconstruction, which can result in fan distortion. In contrast, MRIs retain the accurate geometry of the posterior globe. Therefore, the correlation between NPL from the two modalities suggest that once accounted for, the effect of distortion in OCT does not degrade the reliability of the measurement of NPL. Consequently, OCT may be used to observe NPL with higher resolution and accessibility than at present with MRI.

Comparison between modalities also revealed that OCT with the ILM as a baseline and MRI-derived measures were offset by a bias of approximately 0.4 mm. The bias can be explained by the choice of reference used to calculate NPL in each of the two modalities. The first OCT-derived measure of NPL is obtained using a curve fit of the ILM to estimate a reference level. However, swelling in the RNFL is known to occur with papilledema and as the innermost layer of the RNFL, the ILM would likely be affected. Consequently, the level of the ILM of patients with severe papilledema would be closer to the nerve protrusion compared with the ILM of a control with normal RNFL thickness, resulting in a reference that underestimates the true extent of nerve protrusion. This issue is more relevant in OCT, which has a limited field of view spanning a 6 × 6-mm area around the center of the optic nerve.
head. In contrast, an MRI has a much wider field of view that allows a reference further from the optic nerve head region and further from papilledema-induced swelling. The annular ROI used for the MRI reference is farther away from the center of the optic nerve head. Thus, finding a reference that is less affected by swelling in OCT would provide a NPL more in accordance with measurements derived from MRI. As the outermost layer of the RNFL, the RPE is a commonly used reference in measurements of retinal thickness when examining disease processes such as papilledema and IIH. By using the RPE as a reference, NPL-MRI was closer in magnitude to NPL-OCT and is expected to be less affected by the thickening of the RNFL in the disease state.

Finally, NPL measurements from OCT and MRI were compared with papilledema grades, which revealed significant association with measurements derived from both modalities. A trend for greater extent of nerve protrusion was observed in patients with greater papilledema severity. The current finding is concurrent with work from Alperin et al., which demonstrated correlation between a measure of nerve protrusion derived from MRI and papilledema grade, thereby further supporting nerve protrusion as a clinically relevant marker for papilledema. In this study, measurements of NPL from MRI had greater association with papilledema grade than OCT. Although OCT may have been derived measures of NPL have less overlap between different papilledema grades than OCT. Although OCT may have been expected to show a greater association due to its higher resolution, the results depend on an accurate characterization of papilledema severity using the Frisen scale, a subjective grading system known to produce variation among reviewers. Consequently, the limitations of the Frisen scale may have contributed to the differences in association between OCT measurements of NPL and papilledema severity. Another possible explanation for the greater sensitivity of the MRI measures can be attributed to differences in the derivation of the NPL in each of the two modalities. The MRI measure is based on an average distance while the OCT is based on a maximal distance, which can be more variable. Therefore, future investigations of different OCT-based measures of NPL would be warranted.

In summary, reliable measurements of optic nerve protrusion length can be consistently derived using OCT. The OCT-derived measures were significantly correlated with measurements obtained using MRI and were both strongly associated with papilledema severity. The presence and magnitude of NPL is likely clinically relevant and a more objective measure of papilledema severity than the Frisen scale as it better accounts for the underlying mechanical origin of papilledema.

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References


