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Use of A-scan Ultrasound and Optical Coherence Tomography to Differentiate Papilledema from Pseudopapilledema

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Abstract

Significance—Differentiating papilledema from pseudopapilledema reflecting tilted/crowded optic discs or disc drusen is critical but can be challenging. Our study suggests that SD-OCT peripapillary retinal nerve fiber layer thickness and retrobulbar optic nerve sheath diameter measured by A-scan ultrasound provide useful information when differentiating the two conditions.

Purpose—To evaluate the use of A-scan ultrasound and spectral-domain optical coherence tomography (OCT) retinal nerve fiber layer thickness (RNFL) thickness in differentiating papilledema associated with idiopathic intracranial hypertension from pseudopapilledema.

Methods—Retrospective cross-sectional analysis included 23 papilledema and 28 pseudopapilledema patients. Ultrasound-measured optic nerve sheath diameter (ONSD) at primary gaze, percent change in ONSD at lateral gaze (30° test), and peripapillary RNFLT were analyzed. Receiver operating characteristic (ROC) curves were constructed using one eye from each subject.

Results—Compared to pseudopapilledema, papilledema eyes showed larger mean ONSD (5.4 ± 0.6 vs 4.0 ± 0.3 mm, $p < 0.0001$), greater change(%) of ONSD at lateral gaze (22.4 ± 8.4 vs 2.8 ± 4.8 , $p < 0.0001$), thicker RNFL (219.1 ± 104.6 vs 102.4 ± 20.1 μ m, $p < 0.0001$). ONSD and 30° test had the greatest area under the ROC curve (AUC), 0.98 and 0.97, respectively; followed by inferior quadrant (0.90) and average RNFLT (0.87). All papilledema eyes with Frisén scale > II were accurately diagnosed by ONSD, 30° test or OCT. In mild papilledema (Frisén scale I&II, $n = 15$), AUC remained high for ONSD (0.95) and 30° test (0.93) but decreased to 0.61–0.71 for RNFLT. At 95% specificity, sensitivity (%) for ONSD, 30° test and RNFLT was 91.3, 91.3 and 56.5, respectively for the entire papilledema group; 80.0, 86.7 and 13.3 for the mild papilledema subgroup.

Conclusions—RNFL thickness can potentially be used to detect moderate to severe papilledema. A-scan may further assist differentiation of mild papilledema from pseudopapilledema.

Keywords

papilledema; pseudopapilledema; ultrasound; optical coherence tomography (OCT); optic nerve sheath diameter; retinal nerve fiber layer thickness

Papilledema, optic disc edema secondary to increased intracranial pressure, requires urgent medical management. Ophthalmoscopy is currently the primary tool used for detecting signs of optic disc edema: disc elevation, blurred disc margins, venous congestion, hemorrhages, soft/hard exudates, and choroidal/retinal folds;¹ however, its diagnostic accuracy depends on severity of papilledema and a clinician's expertise. Mild papilledema is easily confused with pseudopapilledema, which includes benign conditions (crowded hyperopic discs, tilted/obliquely inserted discs, buried optic disc drusen) that may mimic disc edema due to overlapping signs (e.g. disc elevation and blurry margin). Systemic and visual symptoms associated with increased intracranial pressure and papilledema such as headache, nausea, vomiting, pulsatile tinnitus, transient visual obscurations, or diplopia are not always present in patients with papilledema; abnormal visual acuity, pupillary responses, color vision or visual field defects (other than enlarged blind spots) are uncommon in acute papilledema. Decision making is further complicated when patients with pseudopapilledema present with unrelated headaches, visual disturbances or visual field defects.² For instance, transient visual obscurations, defined as blurred or loss of vision typically lasting less than 30 seconds and often related to postural changes, is associated with papilledema, but also could occur in crowded optic discs or disc drusen;^{3–5} furthermore, many patients confuse transient visual obscurations with transient visual disturbances from other causes (e.g. dry eye).

To avoid costly and sometimes invasive neurological work-up in patients with pseudopapilledema,⁶ ancillary testing such as optical coherence tomography, orbital ultrasound, and fluorescein angiography has been utilized to improve diagnostic accuracy.^{7–15} Optical coherence tomography has demonstrated increased peripapillary retinal nerve fiber layer thickness in acute papilledema; however, retinal nerve fiber layer thinning occurs in chronic papilledema.^{9, 11–14}

Using ultrasound-measured retrobulbar optic nerve sheath diameter to detect papilledema is based on our understanding of the disease pathogenesis.¹⁶ The retrobulbar portion of the optic nerve sheath is surrounded by orbital fat only, allowing it to expand when the increased cerebrospinal fluid pressure is transmitted to the perioptic subarachnoid space.¹⁷ In 1979, Ossoinig introduced the standardized ophthalmic A-scan to measure optic nerve sheath diameter, and the 30° test for differentiating sheath widening secondary to “fluid” from widening due to “solid” optic nerve lesions such as glioma or meningioma.^{18, 19} When an enlarged optic nerve sheath diameter is encountered at primary gaze, the 30° test is performed by measuring the sheath diameter at lateral (30° or greater) gaze and calculating the percentage change in diameter. In papilledema, a significant reduction of optic nerve sheath diameter occurs at lateral gaze as the optic nerve and its sheath stretches causing redistribution of cerebrospinal fluid over a greater area; as much as a 25% to 30% reduction in sheath distension has been observed.²⁰ The validity of 30° test in detecting increased perioptic cerebrospinal fluid has been shown experimentally in-vitro and in patients

undergoing optic nerve sheath decompression surgery.^{21–23} Retrobulbar optic nerve sheath distention corresponding to elevated cerebrospinal fluid pressure also has been demonstrated by neuro-intensive care providers in patients undergoing intrathecal infusion tests²⁴ or invasive intracranial pressure monitoring using B-scan echography^{17, 25} and magnetic resonance imaging.²⁶

Although both optical coherence tomography and A-scan ultrasound have been shown to be useful, these two techniques have been assessed separately with variable sensitivity and specificity across studies making it difficult to compare the two.^{7–14} Given that performing the standardized A-scan requires great expertise whereas optical coherence tomography is less operator-dependent and widely accessible,²⁷ it is important to evaluate whether A-scan provides additional diagnostic value. The purpose of the current study is to directly compare the diagnostic performance of optical coherence tomography peripapillary retinal nerve fiber layer thickness and two A-scan parameters (optic nerve sheath diameter at primary gaze, and the percentage change in diameter at lateral gaze obtained by the 30° test) in the same patients in order to obtain a better understanding of the strengths and limitations of each technique, and help to establish a diagnostic protocol. In our neuro-ophthalmology clinic, all patients with suspected papilledema or pseudopapilledema underwent comprehensive neuro-ophthalmological exam including spectral domain optical coherence tomography (peripapillary and macular scans), and ophthalmic ultrasound evaluation by an experienced examiner. Although ganglion cell-inner plexiform layer thickness is unlikely to be useful in diagnosing papilledema,²⁸ we included it for analysis as it is a sensitive measure of atrophy in many optic nerve disorders.^{29, 30} To our knowledge, the present study is the first to include both spectral domain optical coherence tomography and standardized A-scan on the same patients.

METHODS

A retrospective review of medical records (2013 – 2015) from the University of Houston MS Eye CARE Clinic identified 23 subjects with papilledema secondary to idiopathic intracranial hypertension and 28 subjects with pseudopapilledema (13 with buried optic disc drusen on B-scan and 15 with oblique optic disc insertion), all referred for presumed papilledema. All patients underwent at least a comprehensive neuro-ophthalmologic examination with dilated fundus examination and optic disc evaluation by the neuro-ophthalmologist (RT), optical coherence tomography, and a referral for ultrasound evaluation that included, for all patients, an initial B-scan to screen for optic disc drusen, and A-scan measurement of optic nerve sheath diameter at primary gaze. The 30° test was performed in those patients with enlarged sheath diameter at primary gaze (see below). Depending on the suspected etiology, further diagnostic work up might have included neurological evaluation with brain/orbital imaging, lumbar puncture, and other necessary tests.⁶ All patients with papilledema had negative neuroimaging and elevated opening pressure on lumbar puncture. For pseudopapilledema patients, 13 showed optic disc drusen on B-scan; 17 had neuroimaging (12 of them performed before referral to the neuro-ophthalmologist), two had lumbar puncture, and six underwent fluorescein angiography to check vascular leakage (a sign associated with disc edema), with normal findings in all. Patients with a previous history of papilledema or those with ocular or systemic conditions

such as retinal/macular disorders, optic nerve disorders other than papilledema/pseudopapilledema, orbital diseases, intracranial tumors that could potentially influence optical coherence tomography or optic nerve sheath diameter measurements were excluded.

All ultrasound examinations were performed by an examiner with 30 years of experience in ophthalmic ultrasound using the Aviso S system (Quantel Medical, Bozeman, MT). B-scan (10 MHz probe) was initially used to detect buried optic disc drusen. Standardized A-scan was used to measure the optic nerve sheath diameter as described by Ossoinig.¹⁹ In brief, a pencil-like A-scan probe (8 mm diameter, unfocused 10 MHz) was placed on the anesthetized bulbar conjunctiva of an open eye temporal to limbus. With the patient initially fixating at primary gaze, the probe was aimed posterior-nasally and slightly superiorly to scan the optic nerve anterior-posteriorly. As shown in Fig. 1A, the optic nerve should appear hollow/empty without major spikes as the parallel fibers do not distort the signal, and be surrounded by spikes of the optic nerve sheath (S_1 and S_2). Through fine adjustment of the probe angling, the examiner obtained maximally high, steeply rising optic nerve sheath spikes that were about equal in amplitude to ensure a true cross-section of the optic nerve, and recorded the most consistent modal measurements (distance between S_1 and S_2). If the optic nerve sheath diameter exceeded the clinically established normal limit (4.2 mm), the dynamic 30° test was performed (Fig. 1B). The patient was instructed to abduct the eye at least 30°, and measurement was repeated several times. The reduction in optic nerve sheath diameter measured at lateral gaze compared to that at primary gaze was calculated as a percentage, with a value of over 20% indicating fluid around the optic nerve, i.e., a positive 30° test. For eyes with normal optic nerve sheath diameter (< 4.2 mm in our case, see an example in Fig. 1C), the 30° test was considered negative as the optic nerve sheath diameter was not expected to change, and a 0% was used for generating the receiver operating characteristic curves. The 4.2 mm and 20% criteria used by the ultrasonographer were previously determined based on his clinical experience in over 100 patients. Future interpretation of the ultrasound test can take account of the cut-off values determined in the current study.

A trained ophthalmic technician performed Cirrus-HD optical coherence tomography 4000 version 6.5 (Carl Zeiss Meditec Inc, Dublin, CA). Average and quadrant peripapillary retinal nerve fiber layer thickness were obtained using the Optic Disc Cube 200 × 200 protocol centered on the optic nerve. The average macular ganglion cell-inner plexiform layer thickness was obtained using the Macular Cube 512 × 128 protocol centered at the fovea. Fig. 2 shows examples of retinal nerve fiber layer and ganglion cell-inner plexiform layer scans in a papilledema patient (Fig. 2A, C) and a pseudopapilledema patient (Fig. 2B, D). All images had signal strength ≥ 7, good centration, and were inspected for segmentation errors.³¹ All patients were included for retinal nerve fiber layer thickness analysis. For ganglion cell-inner plexiform layer thickness analysis, six papilledema patients (both eyes in 3 of them, and the worse eye in the other 3 patients) were excluded due to erroneous segmentation providing artificially thin ganglion cell-inner plexiform layer thickness values. All ganglion cell-inner plexiform layer thickness returned to normal machine range after papilledema resolution.

For each subject, the eye with thicker retinal nerve fiber layer was selected for statistical analysis (STATA 14.1, StataCorp LP, College Station, TX). Two-sample t-test and two proportion z-test were used to compare means and percentages between papilledema and pseudopapilledema groups, respectively. Spearman rho was used to evaluate the relationship between different measurements. Receiver operating characteristic curves were constructed in Sigmaplot 10.0 (Systat Software, Inc).

RESULTS

Of the 51 patients referred in for presumed papilledema, 23 were diagnosed with papilledema (median Frisén scale II) and 28 with pseudopapilledema (13 optic disc drusen and 15 obliquely-inserted discs, Table 1). The diagnosis was made clinically by our experienced neuro-ophthalmologist (RT) based on patient history and ocular/systemic exams including optical coherence tomography and ultrasound data. There was no age difference between the two groups (29.9 ± 11.0 in papilledema vs 28.6 ± 11.8 in pseudopapilledema, $p = 0.69$), but more females (21:2 in papilledema vs 14:14 in pseudopapilledema, $p = 0.0016$) and obese individuals (body mass index > 30) in the papilledema group (78% vs 25% in pseudopapilledema, $p = 0.0002$). Common symptoms in papilledema were headache (91%), transient visual disturbances (61%), and tinnitus (35%). All pseudopapilledema patients had at least one symptom: headache (86%), transient visual disturbances (57%) and tinnitus (21%). No statistical differences existed in the prevalence of the above-mentioned symptoms between the two groups.

The mean optic nerve sheath diameter at primary gaze was larger in papilledema (5.4 ± 0.6 mm) compared to pseudopapilledema (4.0 ± 0.3 mm, $p < 0.0001$) (Table 2). On the 30° test, a larger percent reduction in optic nerve sheath diameter was observed in papilledema (22.4 ± 8.4 %) than in pseudopapilledema (8.6 ± 4.8 % for the 9 eyes with lateral sheath diameters measured, $p < 0.0001$; for the other 19 pseudopapilledema subjects whose sheath diameter at primary gaze were below 4.2 mm, changes were essentially 0%). The mean average retinal nerve fiber layer was thicker in papilledema (219.1 ± 104.6 μm) than in pseudopapilledema (102.4 ± 20.1 μm , $p < 0.0001$), as were quadrant values (Table 2). Abnormal retinal nerve fiber layer thickening ($> 95\%$ of age-matched machine norms) was observed in 56.5% to 87.0% of papilledema eyes, with inferior quadrant showing the most (87.0%) followed by average retinal nerve fiber layer thickness and superior quadrant (69.6% for both). In comparison, only 14.3% to 25.0% of pseudopapilledema eyes showed abnormal retinal nerve fiber layer thickening. After excluding six papilledema eyes with erroneous segmentation (Methods), ganglion cell-inner plexiform layer thickness was slightly decreased in pseudopapilledema (80.9 ± 13.1 μm) when compared to papilledema (86.0 ± 5.5 μm , $p < 0.04$).

Figure 3 shows receiver operating characteristic curves. When all papilledema eyes were included (Fig. 3A), the area under the curve for optic nerve sheath diameter (0.98) and 30° test (0.97) was significantly higher than that (0.87) of average retinal nerve fiber layer thickness ($p = 0.013$ and 0.015 , respectively), but did not reach statistical difference when compared to that (0.90) of inferior retinal nerve fiber layer thickness ($p = 0.05$ and 0.08 , respectively). The optic nerve sheath diameter and 30° test showed the same sensitivity

(91.3%) and specificity (96.4%) with a cutoff value of 4.6 mm and 13.50%, respectively. At 96.4% specificity, the sensitivity was 56.5%, 52.2%, 69.6%, 43.5% and 56.5% for the average, inferior, superior, nasal and temporal retinal nerve fiber layer thickness, respectively (Table 3). Ganglion cell-inner plexiform layer thickness showed no diagnostic value (area under the curve = 0.64, $p = 0.11$). If either optic nerve sheath diameter (> 4.6 mm) or 30° test ($> 13.50\%$) was used for diagnosing papilledema, sensitivity/specificity would be 95.7%/92.9%. Only one (4.3%) papilledema patient who had a normal optic nerve sheath diameter (4.3 mm) and a negative 30° test (3%) was missed by both ultrasound measurements. She was a 35-year-old obese (body mass index = 35) female who presented with headaches, tinnitus, transient visual disturbances, Frisén grade II papilledema, normal average retinal nerve fiber layer thickness (102 μm), thickened ($> 95\%$ age-matched machine norm) inferior retinal nerve fiber layer thickness (176 μm), and elevated lumbar puncture opening pressure (29 cm of H_2O). After treatment, her symptoms improved, average and inferior retinal nerve fiber layer thickness decreased to 96 and 164 μm , respectively.

Knowing that the real diagnostic challenge for eye-care providers lies in differentiating mild papilledema from pseudopapilledema, we compared the 15 papilledema eyes with Frisén scale I and II (if both eyes of an individual met the criteria, the eye with the thinner retinal nerve fiber layer was chosen) to the pseudopapilledema group (in each individual, the eye with thicker retinal nerve fiber layer was chosen). When only mild papilledema eyes were included (Fig. 3B), the ultrasound showed slightly reduced area under the curve and sensitivity (at 96.4% specificity): 0.95 area under the curve and 80% sensitivity for optic nerve sheath diameter, 0.93 and 86.7% for 30° test. However, area under the curve decreased to 0.71, 0.70, 0.64, 0.77, 0.61 for average, inferior, superior, nasal and temporal retinal nerve fiber layer thickness; all significantly worse than that of ultrasound ($p = 0.0005 - 0.029$).

Average retinal nerve fiber layer thickness correlated with optic nerve sheath diameter ($\rho = 0.49$, $p = 0.018$); Frisén scale correlated with lumbar puncture opening pressure ($\rho = 0.48$, $p = 0.019$), optic nerve sheath diameter ($\rho = 0.52$, $p = 0.011$) and average RNFL thickness ($\rho = 0.70$, $p = 0.0002$) (Fig. 4). However, opening pressure was not correlated with sheath diameter ($\rho = 0.01$, $p = 0.95$), 30° test ($\rho = 0.22$, $p = 0.31$), or average retinal nerve fiber layer thickness ($r = 0.17$, $p = 0.44$).

DISCUSSION

Our A-scan ultrasound measurements showed similar sensitivities (91.3%) but higher specificities (96%) than previous reports.^{7, 8} Carter et al⁸ defined abnormal ultrasound using optic nerve sheath diameter (> 3.3 mm) and 30° test ($> 10\%$), reporting a 79% specificity; while Neudorfer et al⁷ only used optic nerve sheath diameter (> 3.3 mm), reporting 63% specificity. If we used $> 10\%$ as a criterion, the 30° test had 91.3%/85.7% sensitivity/specificity. Study population, papilledema severity and variation in ultrasonographer's experience could all contribute to the differences. The optimum cut-off based on the current study was > 4.6 mm for optic nerve sheath diameter and $> 13.5\%$ for 30° test; however, it is crucial for individual examiners to establish their own values.^{19, 32} It is also important for clinicians to integrate clinical history with exam findings and order further testing if there is

a strong suspicion of increased intracranial pressure despite some negative tests. One papilledema patient in our study showed normal optic nerve sheath diameter and a negative 30° test (see details in Results). In some individuals, cerebrospinal fluid along the retrobulbar optic nerve sheath might be minimal despite an increased intracranial pressure, possibly due to a small optic canal.^{16,33}

The diagnostic performance (area under the receiver operating characteristic curve) for retinal nerve fiber layer thickness (0.73 to 0.87) in the current study (0.83 to 0.90) is similar to previous reports (0.73 to 0.87).^{9, 11–13} One Cirrus optical coherence tomography study included patients with buried and surface drusen in pseudopapilledema group and reported higher area under the receiver operating characteristic curve (0.92 to 0.97),¹⁴ which is likely due to thinner retinal nerve fiber layer thickness (88 μm) in their drusen group compared to 102 – 128 μm in current and other studies.^{9, 12, 13} The nasal quadrant retinal nerve fiber layer thickness was suggested by some to have the greatest diagnostic value.^{11–13} No statistical differences existed across quadrants in the current study. Although the area under the receiver operating characteristic curve was highest (0.90) for the inferior quadrant thickness when all papilledema eyes were included, it decreased to 0.70 for mild papilledema eyes.

In our study, both A-scan and optical coherence tomography retinal nerve fiber layer thickness correctly diagnosed all papilledema eyes with Frisén scale III and above. For eyes with mild papilledema (Frisén I & II), the diagnostic performance of A-scan remained high while the area under the receiver operating characteristic curve for retinal nerve fiber layer thickness decreased to 0.61 – 0.77, showing poor performance as previously reported.^{10, 34, 35} Ultrasound's better performance is not surprising. In papilledema, when the perioptic cerebrospinal fluid pressure is mild to moderate, the sheath expansion might balance out some of the pressure rise, leading to only mild or minimal axonal swelling anteriorly. In pseudopapilledema, anatomical changes occur in anterior disc (drusen lie anterior to lamina cribrosa), affecting optical coherence tomography measurements but not the retrobulbar optic nerve sheath.

The Frisén scale was moderately correlated with lumbar puncture opening pressure suggesting a general trend of more severe papilledema in those with higher intracranial pressure. However, a significant correlation between lumbar puncture opening pressure and optic nerve sheath diameter or retinal nerve fiber layer thickness was not observed in our study. It could be that ocular measurements and lumbar puncture were performed at different times, and/or the perioptic pressure differs from the lumbar puncture opening pressure.³⁶ Previous studies have shown optic nerve sheath diameter to be correlated with simultaneous invasively-measured intracranial pressure in neuro-intensive care patients.²⁵

The ganglion cell-inner plexiform layer thickness has proven to have no diagnostic value, consistent with previous reports that this macular change is uncommon in patients with newly diagnosed idiopathic intracranial hypertension and the expectation that axonal swelling does not cause edema in ganglion cell-inner plexiform layer.^{31, 37} It is worth noting that the ganglion cell-inner plexiform layer thickness at the initial visit in 20% ($n = 9/46$) of eyes with papilledema were flagged as “red” (below 99% of the machine normative values)

due to erroneous segmentation, agreeing with the previously reported 20% failure rate of segmentation in papilledema.³⁷ Once the papilledema had resolved, which occurred in all patients, the ganglion cell-inner plexiform layer thickness returned to “normal” when compared to age-matched machine norms. Clinicians and researchers should exercise caution when reporting and monitoring these values.

The sensitivity and specificity of ophthalmoscopy for detecting optic disc edema depends on the examiner’s expertise, signs present and criteria used. Retinal or choroidal folds that are considered pathognomonic for optic disc edema have a low prevalence.¹ Signs such as optic disc elevation, crowding or blurry disc margin are sensitive, but lack specificity (Table 3 in Carta et al 2012).¹ In fact, all of our patients, including the 28 (54.9%, 28/51) diagnosed with pseudopapilledema were initially referred for presumed papilledema based on ophthalmoscopic evaluation by their referring doctors. As detailed ophthalmoscopic signs observed by our neuro-ophthalmologist were not routinely documented during exam, future study should include such fundus signs for further analysis. For primary eye care providers, recognizing ophthalmoscopic signs that might suggest optic disc edema remains crucial for directing further evaluation.

The present study was limited by its retrospective nature, relatively small sample size, potential sampling bias at a tertiary neuro-ophthalmology practice, and the physician being unmasked to ultrasound and optical coherence tomography findings. Compared to Carter et al⁸ where 67% of pseudopapilledema patients were asymptomatic, every pseudopapilledema patient presented with at least one symptom, which was what warranted the referral. Our neuro-ophthalmologist was fully aware that idiopathic intracranial hypertension can occur without papilledema,³⁸ therefore, careful analysis of clinical history, symptomology, and when necessary, further testing, communication with referring neurologists, and observation over time were conducted to minimize false negatives.

Despite the limitations mentioned, our head-to-head comparison between A-scan optic nerve sheath diameter and optical coherence tomography retinal nerve fiber layer thickness demonstrates that both techniques could detect moderate to severe papilledema, and additionally, optic nerve sheath evaluation by a skilled ultrasonographer was useful in differentiating mild cases of papilledema from pseudopapilledema. Knowing that standardized A-scan methodology is difficult to master, we are currently conducting prospective studies to investigate whether equivalent results are achievable using a much simpler and easier-to-learn B-scan technique, and additionally to assess the utility of customized analysis of optical coherence tomography data. Two recent meta-analyses showed that in neuro-intensive units, B-scan-measured optic nerve sheath diameter can differentiate papilledema from normal controls with good sensitivity (90–96%) and specificity (85–92%).^{39, 40} However, these studies reported different optic nerve sheath diameter thresholds, thus internal validation should be performed.

In conclusion, measurement of peripapillary retinal nerve fiber layer thickness by optical coherence tomography, a user-friendly and easily accessible technique, is useful for detecting moderate to severe papilledema. A-scan ultrasound in experienced hands is

valuable for detecting mild papilledema and avoiding unnecessary testing in pseudopapilledema.

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Figure 1.

The A-scan shows the initial probe spike (IP), followed by an area of no spikes, as sound travels through the vitreous (V), then the optic nerve sheath (S1 and S2). The spikes from the sheath should be equal in amplitude and have no major spikes in between them because optic nerves appear hollow/empty as the parallel fibers do not distort the signal. An example of papilledema shows enlarged optic nerve sheath diameter (ONSD) at primary gaze (5.4 mm) (A) that decreases to 4.1 mm (23% reduction) at the 30° gaze (B), presumably due to redistribution of increased subarachnoid fluid over a larger area. An example of pseudopapilledema shows normal ONSD (4.1 mm) at primary gaze (C), for which the 30°

test is not necessary as the optic nerve sheath diameter is not expected to change. The instrument caliper provided the conversion of the X axis scale to mm.

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Figure 2.

Examples of retinal nerve fiber layer (RNFL) and ganglion cell-inner plexiform layer (GCIPL) scans in a papilledema patient (A, C) and a pseudopapilledema patient (B, D). Average RNFL thickness was 125 μ m OD, 138 μ m OS in the papilledema patient (A), thicker than the 95% age-matched machine norm; 97 μ m OD, 94 μ m OS in the pseudopapilledema patient (B), which were within the machine norm. Average GCIPL thickness was 81 μ m in both eyes of the papilledema patient (C) and 79 μ m in both eyes of the pseudopapilledema patient (D), all within the machine normative range.

Figure 3.

Receiver operating characteristic curves for optic nerve sheath diameter (ONSD), 30° test, average (avg) and inferior (Inf) retinal nerve fiber layer (RNFL) thickness in differentiating (A) all papilledema eyes (Frisén I to IV) and (B) mild papilledema eyes (Frisén I & II) from pseudopapilledema.

Figure 4.

Scatterplots showed correlation between average (avg) retinal nerve fiber layer (RNFL) thickness and optic nerve sheath diameter (ONSD) (A: $\rho = 0.49$, $p = 0.018$), Frisén scale and lumbar puncture (LP) opening pressure (B: $\rho = 0.48$, $p = 0.019$). Frisén scale grading correlated with both ONSD (C: $\rho = 0.52$, $p = 0.011$) and avg RNFL thickness (D: $\rho = 0.70$, $p = 0.0002$).

Table 1

Comparison of demographic and clinical characteristics.

	Papilledema (n = 23)	Pseudopapilledema (n = 28)
Age (years) *	29.9±11.0	28.6±11.8
F:M	21:2	14:14
Obese (BMI>30)	18 (78%)	7 (25%)
LP OP (cmH ₂ O) *	31.0±9.9	NA
Buried drusen	NA	13 (46%)
Obliquely-inserted discs	NA	15 (54%)
Frisén scale (n) †	I (3), II (9), III (5), IV (6)	
Symptoms		
Headache	21 (91%)	24 (86%)
TVD	14 (61%)	16 (57%)
Tinnitus	8 (35%)	6 (21%)
Double vision	1 (4%)	0 (0%)
Eye pain	1 (4%)	1 (4%)
Acuity 20/20 or better	23 (100%)	27 (96%)

* mean ± SD;

† based on the worse eye in asymmetrical PE cases;

BMI: body mass index; LP OP: lumbar puncture opening pressure; TVD: transient visual disturbances referring to any transient visual changes reported by patients.

Table 2

Comparisons of ultrasound and OCT findings for papilledema and pseudopapilledema.

	Papilledema (n = 23)	Pseudopapilledema (n = 28)	p
ONSD (mm) at primary gaze	5.4±0.6	4.0±0.3	< 0.0001
ONSD change at 30° gaze (%)	22.4±8.4	8.6±4.8 (n=9) [#]	< 0.0001
% (+) with >10% [*]	91.3	14.3	< 0.0001
% (+) with >13.5% [†]	91.3	3.57	< 0.0001
% (+) with >20% [‡]	82.6	0.00	< 0.0001
Avg RNFL thickness (μm)	219.1±104.6	102.4±20.1	< 0.0001
range (μm)	102–426	60–168	
% thickened [§]	69.6	25.0	0.001
Superior RNFL thickness	277.7±158.7	122.9±31.3	< 0.0001
% thickened [§]	69.6	14.3	0.001
Nasal RNFL thickness	173.6±101.4	80.4±37.4	0.0001
% thickened [§]	65.2	17.9	0.0006
Inferior RNFL thickness	281.0±146.5	136.8±29.7	<0.0001
% thickened [§]	87.0	21.4	<0.0001
Temporal RNFL thickness	121.3±63.6	66.1±13.2	<0.0001
% thickened [§]	56.5	14.3	0.001
GCIPL thickness (μm)	86.0±5.5	80.9±13.1	0.04
% inaccurately segmented	26.1	0.0	

[#]The 30° test was performed in 9 pseudopapilledema eyes whose ONSD at primary gaze exceeded 4.2 mm (mean 4.4±0.1, n=9), and was considered negative with essentially 0% change for the other 19 pseudopapilledema eyes whose ONSD at primary gaze was below 4.2 mm.

^{*}a commonly suggested criterion²⁰;

[†]based on receiver operating characteristic curve analysis (Table 3);

[‡]based on our ultrasonographer's experience;

[§]thicker than the 95% age-matched machine norms;

OCT: optical coherence tomography; ONSD: optic nerve sheath diameter; Avg RNFL thickness: average retinal nerve fiber layer thickness; GCIPL: ganglion cell- inner plexiform layer thickness

Table 3

AUC and various cutoff values with their respective sensitivity (Sen) and specificity (Spec) for ultrasound and OCT in differentiating papilledema from pseudopapilledema

	AUC (95% CI)	Sen/Spec (cutoff)	Sen@95%Spec (cutoff)	Spec@95%Sen (cutoff)
ONSD	0.98 (0.95–1.00)	91.3/96.4 (4.6 mm)	91.3 (4.6 mm)	78.1 (4.4 mm)
30° test	0.97 (0.94–1.01)	91.3/96.4 (13.5%)	91.3 (13.5%)	71.4 (3.5%)
Avg RNFL thickness	0.87 (0.77–0.96)	73.9/75.0 (107.0 µm)	56.5 (156.0 µm)	50.0 (102.0 µm)
S	0.83 (0.71–0.95)	73.9/78.6 (141.5 µm)	69.6 (163.5 µm)	28.6 (101.0 µm)
N	0.83 (0.71–0.95)	78.3/75.0 (81.5 µm)	43.5 (197.0 µm)	28.6.0 (66.0 µm)
I	0.90 (0.82–0.98)	87.0/75.0 (147.5 µm)	52.2 (213.5 µm)	67.9 (140.5 µm)
T	0.84 (0.73–0.96)	78.3/82.1 (73.5 µm)	56.5 (93.5 µm)	25.0 (61.0 µm)

Sen/Spec: Sensitivity/Specificity in %; Sen@95%Spec: Sensitivity at 95% Specificity; Spec@95%Sen: Specificity at 95% Sensitivity; AUC: area under the receiver operating characteristic curve; ONSD: optic nerve sheath diameter; Avg RNFL thickness: average retinal nerve fiber layer thickness; S, N, I, T: superior, nasal, inferior, and temporal quadrant retinal nerve fiber layer thickness