Major Article

Bruch's membrane opening on optical coherence tomography in pediatric papilledema and pseudopapilledema

Atalie C. Thompson, MD, MPH,[a] M. Tariq Bhatti, MD,[a,b,c] and Mays A. El-Dairi, MD[a]

PURPOSE To determine whether the diameter of Bruch's membrane opening (BMO) can distinguish mild papilledema from pseudopapilledema using optical coherence tomography (OCT).

METHODS The medical records of pediatric patients with pseudopapilledma due to optic nerve head (ONH) drusen, patients with papilledema, and normal control subjects were retrospectively reviewed. All eyes underwent OCT imaging of the BMO and retinal nerve fiber layer (RNFL). Transverse horizontal diameter of the BMO and papillary height were measured. Mean BMO, papillary height, and RNFL were compared and receiver operating characteristic (ROC) curves were used to calculate the area under the curve (AUC) and determine BMO and RNFL cut-offs for papilledema and pseudopapilledema.

RESULTS A total of 90 eyes of 90 subjects were included: 58 with pseudopapilledema, 19 with papilledema, and 13 controls. In eyes with papilledema, mean BMO, papillary height, and RNFL decreased as papilledema resolved (1893.8 vs 1582.2 [$P = 0.0003$], 193.0 vs 108.9 [$P < 0.0001$], 893.3 vs 695.5 [$P = 0.0007$], resp.). Eyes with mild papilledema had greater mean BMO and RNFL than those with pseudopapilledema and controls (1893.8 vs 1541.9 vs 1628.8 [$P < 0.0001$, $P = 0.0265$] and 193.0 vs 108.7 vs 104.1 [$P < 0.0001$, $P < 0.0001$], resp.). Papillary height in mild papilledema was similar to pseudopapilledema but greater than controls (893.3 vs 863.2 vs 593.5 [$P = 0.47$ and $P = 0.0001$], resp.). ROC showed good diagnostic discrimination for BMO (AUC = 0.81; 95% CI, 0.70-0.92) and RNFL (AUC = 0.96; 95% CI, 0.93-1.0) in distinguishing mild papilledema from pseudopapilledema.

CONCLUSIONS The horizontal transverse diameter of BMO is enlarged in eyes with mild papilledema and narrows as papilledema resolves. BMO and RNFL can be used together to help distinguish mild papilledema from pseudopapilledema in children. (J AAPOS 2017;■:1-6)

Patients with low-grade papilledema can present a diagnostic challenge. Absence of spontaneous venous pulsations, common in conditions that raise intracranial pressure (ICP), may also be present in 10% of healthy patients[1] and can be associated with full disks that lack a cup[2] or that have optic nerve head (ONH) drusen.[3] Clinically distinguishing mild disk edema from pseudopapilledema due to ONH drusen can be particularly challenging because appearance of the ONH can overlap between these two distinct entities.

Spectral domain optical coherence tomography (SD-OCT) is useful in assessing the dimensions of the ONH and the thickness of the retinal nerve fiber layer (RNFL) in multiple conditions, including papilledema and pseudopapilledema.[4-7] Quantification of the peripapillary RNFL is widely used to help diagnose and monitor response to treatment of papilledema from idiopathic intracranial hypertension (IIH).[5,6,8-13] Several studies have suggested that raised ICP may lead to mechanical deformation of the connective tissues surrounding the ONH, including the lamina cribrosa and Bruch's membrane.[7,8,10,14,15] Villaruell and colleagues[7] demonstrated that the lamina cribrosa is positioned anteriorly in IIH and posteriorly in glaucomatous eyes relative to controls, presumably due to the translaminar pressure difference. Similarly, the retinal pigment epithelium–Bruch's membrane (RPE/BM) layer has been shown to angulate inward in a proportion of eyes with papilledema but not in eyes with nonarteritic ischemic optic neuropathy.[8,10,15] Several studies have also sought to characterize the opening in the termination of the Bruch's membrane around the optic nerve in glaucoma,[16-18] tilted disks,[19] and normal aging adult eyes.[20-22] To our knowledge, the transverse horizontal opening in Bruch's membrane has not been

Author affiliations: Departments of Ophthalmology[a], Neurology[b], and Neurosurgery[c], Duke Eye Center and Duke University Medical Center, Durham, North Carolina

Submitted May 27, 2017.
Revision accepted September 17, 2017.

Correspondence: Mays A. El-Dairi, MD, 2351 Erwin Road, Hudson Room 4527, Durham, NC 27705, PO box 3802 (email: mays.el-dairi@duke.edu).

1091-8531/$36.00
https://doi.org/10.1016/j.jaapos.2017.09.003

compared in subjects with low-grade papilledema and pseudopapilledema. Moreover, few studies have examined the characteristics of the ONH on OCT in a pediatric population with IIH or ONH drusen.[23-25] We hypothesized that the size of the transverse horizontal diameter of the opening in Bruch's membrane (BMO) can help to distinguish low-grade papilledema from pseudopapilledema on OCT in children. This study also sought to determine whether combining average RNFL and BMO improved the sensitivity and specificity of OCT for distinguishing mild papilledema from pseudopapilledema.

Subjects and Methods

This study was approved by the Institutional Review Board of Duke University Medical Center and conformed to the requirements of the US Health Insurance Portability and Accountability Act of 1996. Patients ≤18 years of age who presented at the pediatric ophthalmology and neuro-ophthalmology clinics of the Duke Eye Center between August 1, 2011, and August 1, 2017, and who had been enrolled in a prospective pediatric study on SD-OCT were considered for inclusion; subjects comprised patients diagnosed with papilledema due to idiopathic intracranial hypertension, those with pseudopapilledema due to ONH drusen, and healthy controls. Written informed consent for collection of OCT imaging was obtained as part of the prospective study. Imaging and medical records of subjects were reviewed retrospectively. Additional data collected included age, sex, race, lumbar puncture opening pressure, presence of spontaneous venous pulsations on dilated examination, and imaging findings on magnetic resonance imaging (MRI), B-scan, fluorescein angiography, or fundus autofluorescence.

All subjects underwent a complete ophthalmic examination, including dilated fundus examination by a pediatric neuro-ophthalmologist (MAE-D), with grading of ONH swelling on the Frisén scale.[26] Baseline fundus photographs and SD-OCT images (Spectralis, Heidelberg, Carlsbad, CA) of both ONHs and RNFL were obtained. Both enrolled and unenrolled eyes with any of three diagnoses were retrospectively reviewed by examiners (MAE-D, ACT) masked to the diagnosis, enrollment, and examination findings.

To be included, subjects with IIH had to have been diagnosed when <18 years of age, have a dilated examination documenting mild papilledema (grade 1-2), and meet the revised diagnostic criteria for IIH proposed by Friedman, Liu, and Digre.[27]

Subjects with pseudopapilledema had to have (1) presence of spontaneous venous pulsations as observed by a pediatric neuro-ophthalmologist (MAE-D) or normal MRI or lumbar puncture and (2) longitudinal stability of the ONH on examination and imaging in at least 2 visits over 6 months. Eyes with pseudopapilledema had an ONH drusen identified with OCT imaging during masked review (Figure 1A) and confirmed with additional imaging findings (e.g., echogenicity on B-scan, hyperautofluorescence on fundus autofluorescence, or absence of leakage on fluorescein angiography). Fundus images were reviewed for the presence of visible surface drusen. The OCT images of papilledema subjects were reviewed by two masked readers (MAE-D, ACT) to assess for the interval development of buried hyperreflective material after their papilledema had resolved, because this could be consistent with ONH drusen. Subjects diagnosed with another ophthalmic condition affecting the optic nerve, such as glaucoma, ocular hypertension, optic neuropathy, or anomalous ONH were excluded. Optic nerves with anomalous branching of vessels were not excluded. Subjects presenting with optic atrophy were excluded, because their presentation would not be consistent with pseudopapilledema.

The average thickness of the circumferential RNFL was calculated using manufacturer software provided with the SD-OCT. Segmentation errors for RNFL were manually corrected by the senior author (see eFigure 1). The BMO was defined as the horizontal transverse diameter of the neural canal opening (in micrometers) at the level of the RPE/BM.[8] Papillary height was defined as a vertical line from the highest point of the ONH to the BMO/BM.[8] For subjects with IIH, measurements were taken at the time they had grade 1-2 papilledema and when their papilledema had resolved (Figure 2). Angulation of the BMO was categorized as positive (ie, RPE/BM angulated inward toward vitreous) or negative (ie, RPE/BM neutral or angulated outward).[10] All BMO and papillary height measurements were taken with the measurement tool in the Heidelberg-Spectralis software by an ophthalmologist experienced in OCT who was masked to the ICP data and diagnosis (ACT).

Statistical Analysis

The overall difference in baseline demographic variables between subjects with mild papilledema, pseudopapilledema, and controls were assessed by χ^2 test and analysis of variance. A single eye in an initial cohort (presenting August 1, 2011, through November 1, 2017) was analyzed, using the following rubric if both eyes met inclusion criteria: odd birth year, right eye; even, left eye. The three characteristics of the ONH—average RNFL, BMO, and papillary height—were compared by age, race, and sex. A paired t test was used to compare the ONH characteristics when subjects with IIH had low-grade papilledema and when it had resolved. The ONH characteristics were also compared between subjects with mild papilledema and those with pseudopapilledema or with controls. Receiver operating characteristic (ROC) curves were graphed to calculate the area under the curve (AUC) and determine cut-offs for BMO, RNFL, papillary height, and Bruch's membrane angulation to discriminate between subjects with papilledema versus pseudopapilledema. Multivariate logistic regression was used to assess the strength of association between mild papilledema versus pseudopapilledema, and the cut-offs for BMO and RNFL. A subanalysis was also performed excluding subjects with papilledema that developed hyperreflective material beneath the ONH on OCT when papilledema had resolved. The cut-offs generated by the initial cohort were used to classify the eyes of a second cohort of subjects (January 1, 2017, through August 1, 2017) with either pseudopapilledema due to ONH drusen or papilledema due to IIH. This second cohort met the same inclusion/exclusion criteria and underwent the same aforementioned