

Imaging Optic Nerve Head Drusen With Spectral Domain OCT

A new algorithm may help clinicians to determine the cause of visual field loss in patients with coexisting drusen and glaucoma.

BY HUIJUAN WU, MD, PhD; JOHANNES F. DE BOER, PhD; AND TERESA C. CHEN, MD

Drusen of the optic nerve head are an uncommon but serious cause of visual loss. Although these laminated calcified hyaline bodies^{1,2} are often asymptomatic,³ they may cause progressive visual field loss¹ by disrupting axonal metabolism⁴ or altering axoplasmic transport.² Ischemia from optic nerve head drusen has also been reported to cause acute visual loss.⁵ The clinical incidence of optic nerve head drusen is 3.4 to 4.9 per 1,000 individuals,¹ but evidence from autopsies suggests that these lesions are present in 20.4 of every 1,000 individuals.⁶

Clinically, optic nerve head drusen appear as elevations of the optic disc that may be confused with papilledema or swelling of the optic nerve head.⁷ These lesions often obscure the margins of the optic disc and give it an irregular appearance.⁷⁻⁹ Because optic nerve head drusen present diagnostic dilemmas and have a potentially poor prognosis, finding a reliable and accurate method for detecting these lesions is crucial.

The current methods of diagnosing optic nerve head drusen include direct visualization with ophthalmoscopy, fundus photography (Figure 1A), autofluorescence with fluorescein angiography (Figure 1B), computerized tomography, and B-scan ultrasonography (Figure 1C). Of these modalities, ultrasonic testing has proven the most sensitive.^{10,11} These techniques only detect the presence of optic nerve head drusen, however, and do not provide information about their shape, size, or location.

The presence of optic nerve head drusen in patients who also have glaucoma confounds clinicians' ability to diagnose and track the progression of both conditions.^{7,12} Furthermore, clinicians may have difficulty attributing progressive visual field loss to optic nerve head drusen versus glaucoma, because both conditions appear as thinning of the retinal nerve fiber layer on time-domain optical coherence tomography (OCT).^{7,9,13-15}

These diagnostic quandaries highlight the inadequacy of current imaging techniques for assessing optic nerve head

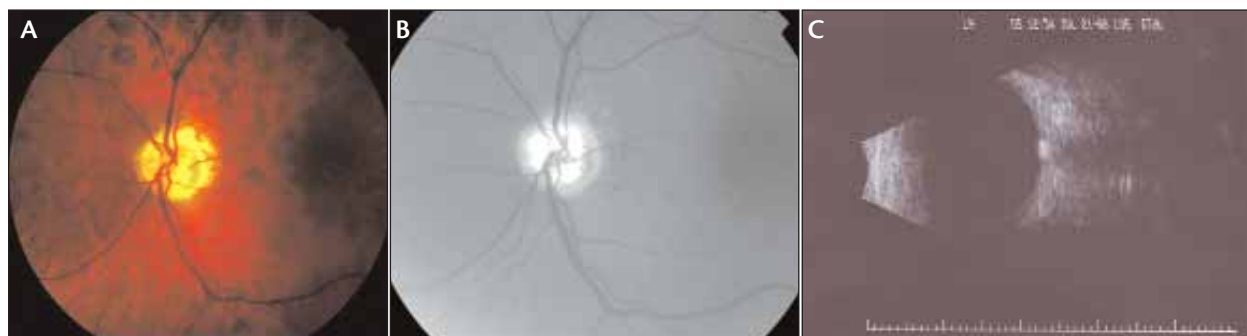


Figure 1. Drusen are apparent on the left optic nerve of a patient with coexisting glaucoma (A). Fluorescein angiography highlights the drusen in the same patient (B). Drusen characteristically appear as highly reflective oval structures with acoustic shadowing on B-scan ultrasonography (C). (Reprinted with permission from Yi K, Mujat M, Sun W, et al. Imaging of optic nerve head drusen: improvements with spectral domain optical coherence tomography. *J Glaucoma*. 2009;18:373-378.)

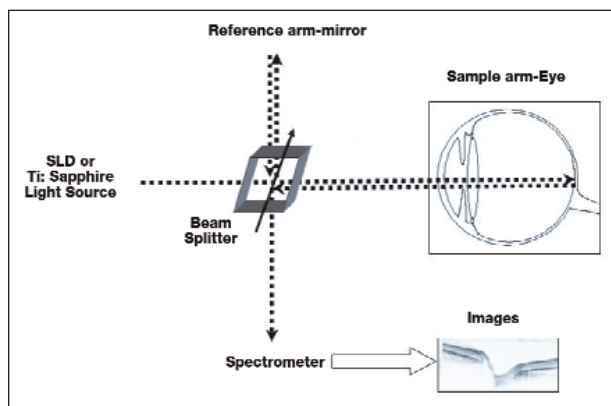


Figure 2. Schematic of imaging with SD-OCT. Abbreviations: SLD, superluminescent diode; Ti, titanium. (Reprinted with permission from Yi K, Mujat M, Sun W, et al. Imaging of optic nerve head drusen: improvements with spectral domain optical coherence tomography. *J Glaucoma*. 2009;18:373-378.)

drusen. We are using spectral domain OCT (SD-OCT) to obtain much-needed quantitative information about these potentially sight-threatening lesions.

TECHNOLOGICAL OVERVIEW

SD-OCT (also called *Fourier-domain OCT*) is a new technology that can obtain ultra-high-resolution images ($2\ \mu\text{m}$ vs $10\ \mu\text{m}$ with time-domain OCT)¹⁶⁻¹⁸ of ophthalmic tissues at the rate of 29,000 A-lines per second.¹⁹⁻²¹ This unprecedented speed allows SD-OCT to image square $6\ \text{X}\ 6\text{-mm}$ or rectangular $8.85\ \text{X}\ 5.73\text{-mm}$ areas of the posterior pole.²¹⁻²³

Johannes F. de Boer, PhD, developed the first prototypic video-rate SD-OCT at the Massachusetts General Hospital, Wellman Center for Photomedicine, and Dr. Chen conducted clinical studies with the device at the Massachusetts Eye and Ear Infirmary.^{21, 24-26} This device obtains images by splitting the light emitted by a superluminescent diode or a titanium:sapphire laser into two beams. One beam is directed toward a reference mirror and the other toward the eye (Figure 2).

As the source beams reflect off the eye and reference mirror, they create an interference pattern that is captured and analyzed by a spectrometer in the device's detector arm. Composed of the transmission grating and the air-spaced focusing lens, the spectrometer analyzes the interference patterns in a spectrum of mixed reflected lights to obtain depth information of targeted tissue.^{17,24} Finally, these data undergo Fourier transformation to produce an image of the targeted ophthalmic structures.^{21,24}

Whereas commercially available time-domain OCT systems such as the Stratus OCT3 (Carl Zeiss Meditec, Inc., Dublin, CA) are limited to a two-dimensional output, SD-OCT can create three-dimensional images of

ocular structures. SD-OCT's advanced imaging capability is possible, because its scanning speed is 72 times more efficient than that of time-domain OCT.²³

By the end of 2006, the FDA had cleared the first commercially available SD-OCT systems for clinical use in the United States. Since then, several companies have introduced their versions of the technology. Examples of available instruments include the Cirrus HD-OCT (Carl Zeiss Meditec, Inc.), RTVue-100 (Optovue, Inc., Fremont, CA), Spectral OCT/SLO (OTI, Toronto, Ontario, Canada), Spectralis (Heidelberg Engineering GmbH, Heidelberg, Germany), SOCT Copernicus (Reichert Ophthalmic Instruments, Inc., Depew, NY), and 3D OCT-1000 (Topcon Medical Systems, Inc., Paramus, NJ). Unfortunately, none of these devices has algorithms that determine the size, shape, or location of optic nerve head drusen.

In a pilot study at the Massachusetts Eye and Ear Infirmary, Dr. Chen and colleagues tested the feasibility of a novel algorithm for imaging optic nerve head drusen. This algorithm was designed to overcome the shortfalls of other imaging techniques. The results of this study follow.

IMAGING OF OPTIC NERVE HEAD DRUSEN Quantitative Information

Dr. de Boer and colleagues have developed an algorithm that, when used with SD-OCT, determines the shape and location of optic nerve head drusen. This algorithm also calculates the volume of the lesions, a measurement that the investigators found was directly correlated with absolute values of mean deviation with Humphrey visual field testing (Carl Zeiss Meditec, Inc.) in eyes with optic nerve head drusen and glaucoma.²⁷

The volunteers for Dr. Chen's study included one patient with optic nerve head drusen who underwent exenteration surgery for orbital melanoma and four patients with concomitant optic nerve head drusen and glaucoma. After evaluating the volunteers with Dr. de Boer's prototypic SD-OCT system, the investigators used an experimental algorithm (commercially available software from Amira [Mercury Computer Systems Inc., Chelmsford, MA] interfaced with open-source C++ algorithms from Insight Registration and Segmentation Toolkit [available at <http://www.itk.org/>]) to translate the data into three-dimensional images.

Correlation With Histology

An analysis of the patient with orbital melanoma allowed the investigators to correlate images of optic nerve head drusen obtained with time-domain and SD-OCT with the histology of the patient's exenterated eye. The optic nerve head drusen are visible on fundus photography as a promi-

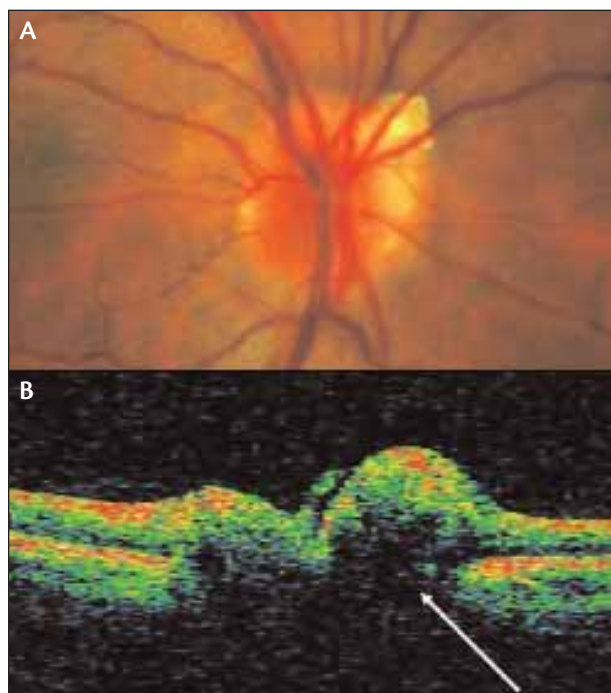


Figure 3. Fundus photography of the right eye of a patient with bilateral optic nerve head drusen shows a prominent lesion at the superior nasal border of the optic nerve head (A). Imaging of the same eye with time-domain OCT shows a region of decreased signal (arrow) below the surface of the elevated optic nerve head. (Reprinted with permission from Yi K, Mujat M, Sun W, et al. Imaging of optic nerve head drusen: improvements with spectral domain optical coherence tomography. *J Glaucoma*. 2009;18:373-378.)

nence in the superior nasal border of the optic nerve head (Figure 3A). Time-domain OCT shows the mass as an elevation of the optic nerve head and an area of decreased signal below its surface (Figure 3B).

Despite the poor quality of the images obtained with time-domain OCT, histology of the exenterated eye confirmed the presence of a large, lobulated, optic nerve head drusen above the level of the lamina cribrosa (Figure 4A). The lesions were clearer with SD-OCT than with time-domain OCT, and they appeared as regions of poor signal intensity surrounded by highly reflective borders (Figure 4B). When the experimental algorithm processed the data from the SD-OCT device, the resulting map showed the drusen's three-dimensional borders (Figure 4C and D).

The investigators were also able to determine that the volume of the lesion was 0.0304 mm^3 . This case demonstrates a good correlation between three-dimensional images obtained with SD-OCT (Figure 4B to D) and the histopathological analysis of optic nerve head drusen.

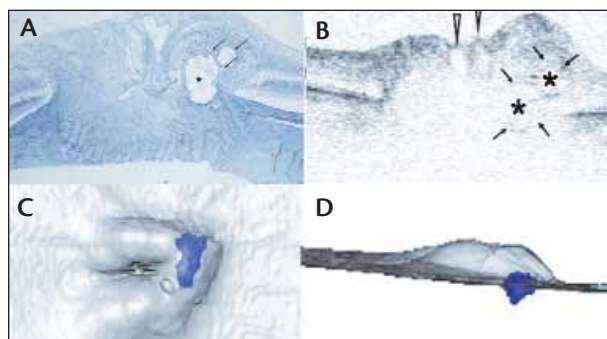


Figure 4. Histology of the same eye from Figure 3 shows a large, lobulated drusen (asterisk) and smaller lesions (arrows) above the level of the lamina cribrosa. Much of the drusen's calcific substance was lost during processing (magnification X 50, Toluidine blue staining) (A). SD-OCT images obtained before exenteration surgery show drusen as regions of poor signal intensity (asterisks) surrounded by highly reflective borders (arrows). Circular structures visible near the surface of the optic nerve head were continuously detected in serial images and were therefore confirmed as blood vessels (arrowheads) (B). Three-dimensional reconstructions of the optic nerve created with the experimental algorithm show drusen (blue) within the nasal border of the optic nerve head. The drusen were also visible through the transparent surface of the optic nerve head (C). A three-dimensional reconstruction viewed from a different angle revealed the spatial relationship between the surface of the optic disc and the drusen (blue) (D). (Reprinted with permission from Yi K, Mujat M, Sun W, et al. Imaging of optic nerve head drusen: improvements with spectral domain optical coherence tomography. *J Glaucoma*. 2009;18:373-378.)

Correlation With Perimetry

The pilot study conducted at the Massachusetts Eye and Ear Infirmary also showed a strong correlation between the experimental algorithm and functional testing with the Humphrey visual field analyzer 750i (24-2 Swedish interactive thresholding algorithm standard program, Carl Zeiss Meditec, Inc.) The investigators observed an excellent positive correlation between the volume of the optic nerve head drusen (mm^3) and the magnitude of the mean deviation (dB) derived from visual field testing ($r^2 = 0.97$).

Although the new SD-OCT algorithm provided better quantitative information about optic nerve head drusen than time-domain OCT, it did not clearly indicate whether a visual field defect was caused by the pathologic lesion or glaucoma. For example, the investigators detected optic nerve head drusen measuring 0.0467 mm^3 in the right eye of a 50-year-old glaucoma patient. Because three-dimensional images showed the lesion in the nasal aspect of the optic nerve head, the investigators suggested that the inferi-

or nasal defect detected with ancillary perimetry was more likely associated with glaucomatous progression.

This patient's visual field defect could have been caused by the optic nerve head drusen; however, because several studies note that the location of visible lesions is not always correlated with observed changes in visual function.²⁸⁻³⁰ In such cases, visual field defects may be the result of axonal compression by drusen deep in the optic nerve or above the lamina cribrosa^{28,31} or a vascular event.^{8,32} Ultimately, a longitudinal evaluation of this 50-year-old patient's visual fields and the volume of the optic nerve head drusen may clarify whether further visual field loss is due to an increase in the lesion's volume or to glaucomatous progression.

The pilot study also included a glaucoma patient who had optic nerve head drusen that measured 0.839 mm³ and encompassed almost 360° of the optic nerve head in his left eye. In this case, the investigators concluded that the generalized depression on Humphrey visual field testing was more likely due to the drusen than the patient's glaucoma.

Future studies of the new SD-OCT algorithm in larger patient populations may better elucidate the primary mechanism by which drusen cause visual field defects, especially lesions that are buried below the surface of the optic nerve head.

CONCLUSION

Initially asymptomatic, drusen of the optic nerve head are a sight-threatening disease that can be easily overlooked by clinicians and patients. A new algorithm developed for SD-OCT provides valuable quantitative information about these lesions and may improve clinicians' ability to determine the underlying cause of visual field loss in patients with coexisting optic nerve head drusen and glaucoma. □

Teresa C. Chen, MD, is an associate professor of ophthalmology at the Massachusetts Eye and Ear Infirmary, Harvard Medical School, Boston. She acknowledged no financial interest in the products or companies mentioned herein. Dr. Chen may be reached at 617-573-3674; teresa_chen@meei.harvard.edu.



Johannes F. de Boer, PhD, is a professor of physics and astronomy at the VU University, Amsterdam, The Netherlands. He holds patents for SD-OCT and has received research support from Nidek. Dr. de Boer may be reached at +31 20 5987972; jfdeboer@few.vu.nl.



Huijuan Wu, MD, PhD, is an attending doctor of ophthalmology at Peking University, People's Hospital, Beijing, China. She acknowledged no financial interest in the products or companies



mentioned herein. Dr. Wu may be reached at drhuijuanwu@yahoo.com; +86 10 88325413.

1. Lee AG, Zimmerman MB. The rate of visual field loss in optic nerve head drusen. *Am J Ophthalmol*. 2005;139(6):1062-1066.
2. Spencer WH. XXXIV Edward Jackson Memorial Lecture: drusen of the optic disc and aberrant axoplasmic transport. *Ophthalmology*. 1978;85(1):21-38.
3. Wilkins JM, Pomeranz HD. Visual manifestations of visible and buried optic disc drusen. *J Neuroophthalmol*. 2004;24(2):125-129.
4. Tso MO. Pathology and pathogenesis of drusen of the optic nerve head. *Ophthalmology*. 1981;88(10):1066-1080.
5. Beck RW, Corbett JJ, Thompson HS, et al. Decreased visual acuity from optic disc drusen. *Arch Ophthalmol*. 1985;103(8):1155-1159.
6. Friedman AH, Gartner S, Modi SS. Drusen of the optic disc: a retrospective study in cadaver eyes. *Br J Ophthalmol*. 1975;59(8):413-421.
7. Auw-Haendrich C, Staubach F, Witschel H. Optic disc drusen. *Surv Ophthalmol*. 2002;47(6):515-532.
8. Roh S, Noecker RJ, Schuman JS, et al. Effect of optic nerve head drusen on nerve fiber layer thickness. *Ophthalmology*. 1998;105(5):878-885.
9. Davis PL, Jay WM. Optic nerve head drusen. *Semin Ophthalmol*. 2003;18(4):222-242.
10. Boldt HC, Byrne SF, DiBernardo C. Echographic evaluation of optic disc drusen. *J Clin Neuroophthalmol*. 1991;11(2):85-91.
11. Kurz-Levin MM, Landau K. A comparison of imaging techniques for diagnosing drusen of the optic nerve head. *Arch Ophthalmol*. 1999;117(8):1045-1049.
12. Roh S, Noecker RJ, Schuman JS. Evaluation of coexisting optic nerve head drusen and glaucoma with optical coherence tomography. *Ophthalmology*. 1997;104(7):1138-1144.
13. Dinakaran S, Talbot JF. Optic disc drusen associated with neovascularization of optic disc. *Eye*. 2005;19(7):816-818.
14. Ocakoglu O, Ustundag C, Koyluoglu N. Long term follow-up of retinal nerve fiber layer thickness in eyes with optic nerve head drusen. *Curr Eye Res*. 2003;26(5):277-280.
15. Floyd MS, Katz BJ, Digre KB. Measurement of the scleral canal using optical coherence tomography in patients with optic nerve drusen. *Am J Ophthalmol*. 2005;139(4):664-669.
16. Cense B, Chen TC, Nassif N, et al. Ultra-high speed and ultra-high resolution spectral-domain optical coherence tomography and optical Doppler tomography in ophthalmology. *Bull Soc Belge Optalmol*. 2006;302:123-132.
17. Wojtkowski M, Srinivasan V, Fujimoto JG, et al. Three-dimensional retinal imaging with high-speed ultrahigh-resolution optical coherence tomography. *Ophthalmology*. 2005;112(10):1734-1746.
18. Schmidt-Erfurth U, Leitgeb RA, Michels S, et al. Three-dimensional ultrahigh-resolution optical coherence tomography of macular diseases. *Invest Ophthalmol Vis Sci*. 2005;46(9):3393-3402.
19. Mujat M, Chan R, Cense B, et al. Retinal nerve fiber layer thickness map. *Opt Express*. 2005;13:9480-9491.
20. Nassif N, Cense B, Park BH, et al. In vivo human retinal imaging by ultrahigh-speed spectral domain optical coherence tomography. *Opt Letters*. 2004;29:480-482.
21. Chen TC, Cense B, Pierce MC, et al. Spectral domain optical coherence tomography: ultrahigh-speed, ultrahigh-resolution ophthalmic imaging. *Arch Ophthalmol*. 2005;123(12):1715-1720.
22. Gabriele ML, Ishikawa H, Wollstein G, et al. Optical coherence tomography scan circle location and mean retinal nerve fiber layer measurement variability. *Invest Ophthalmol Vis Sci*. 2008;49(6):2315-2321.
23. Chen TC, Zeng A, Sun W, et al. Spectral domain optical coherence tomography and glaucoma. *Int Ophthalmol Clin*. 2008;48(4):29-45.
24. Yi K, Chen TC, de Boer JF. Spectral domain optical coherence tomography. *Tech Ophthalmol*. 2006;4:170-174.
25. de Boer JF, Cense B, Park BH, et al. Improved signal-to-noise ratio in spectral-domain compared with time-domain optical coherence tomography. *Opt Lett*. 2003;28(21):2067-2069.
26. Nassif N, Cense B, Park BH, et al. In vivo human retinal imaging by ultrahigh-speed spectral domain optical coherence tomography. *Opt Lett*. 2004;29(5):480-482.
27. Yi K, Mujat M, Sun W, et al. Imaging of optic nerve head drusen: improvements with spectral domain optical coherence tomography. *J Glaucoma*. 2009;18:373-378.
28. Auw-Haendrich C, Staubach F, Witschel H. Optic disc drusen. *Surv Ophthalmol*. 2002;47(6):515-532.
29. Pollack IP, Becker B. Hyaline bodies (drusen) of the optic nerve. *Am J Ophthalmol*. 1962;54:651-654.
30. Digre KB, Corbett JJ. Is swelling present in the disc? In: Digre KB, Corbett JJ, eds. *Practical Viewing of the Optic Disc*. Burlington, VT: Elsevier Health Sciences; 2003:105-192.
31. Brodsky MC. Congenital anomalies of the optic disc. In: Miller NR, Newman NJ, eds. *Walsh & Hoyt's Clinical Neuro-Ophthalmology*. 6th ed. Philadelphia, PA: Lippincott, Williams & Wilkins; 2005:151-196.
32. Sarkies NJ, Sanders MD. Optic disc drusen and episodic visual loss. *Br J Ophthalmol*. 1987;71(7):537-539.