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Assessment of Optic Nerve Head Drusen Using Enhanced Depth Imaging and Swept Source Optical Coherence Tomography

Anna L. Silverman, BA, **Andrew J. Tatham, FRCOphth**, **Felipe A. Medeiros, MD, PhD**, and **Robert N. Weinreb, MD**

Department of Ophthalmology, Hamilton Glaucoma Center, University of California, San Diego, California

Abstract

Background—Optic nerve head drusen (ONHD) are calcific deposits buried or at the surface of the optic disc. Although ONHD may be associated with progressive visual field defects, the mechanism of drusen-related field loss is poorly understood. Methods for detecting and imaging disc drusen include B-scan ultrasonography, fundus autofluorescence, and optical coherence tomography (OCT). These modalities are useful for drusen detection but are limited by low resolution or poor penetration of deep structures. This review was designed to assess the potential role of new OCT technologies in imaging ONHD.

Evidence Acquisition—Critical appraisal of published literature and comparison of new imaging devices to established technology.

Results—The new imaging modalities of enhanced depth imaging optical coherence tomography (EDI-OCT) and swept source optical coherence tomography (SS-OCT) are able to provide unprecedented in vivo detail of ONHD. Using these devices it is now possible to quantify optic disc drusen dimensions and assess integrity of neighboring retinal structures, including the retinal nerve fiber layer.

Conclusions—EDI-OCT and SS-OCT have the potential to allow better detection of longitudinal changes in drusen and neural retina and improve our understanding of drusen-related visual field loss.

Optic nerve head drusen (ONHD) are acellular deposits of calcium, amino and nucleic acids, and mucopolysaccharides, buried or at the surface of the optic disc (1–3). When located near the surface, drusen can be directly visualized by ophthalmoscopy. Superficial drusen typically confer an irregular lumpy appearance to the optic disc (4). It is hypothesized that some superficial drusen become visible with age as a result of drusen growth or loss of the neural tissue that obscures the drusen. In contrast, when disc drusen are located closer to the lamina cribrosa, they can be difficult to detect and may require imaging for confirmatory diagnosis (5,6). Although ONHD are normally asymptomatic, they are associated with visual field defects in 24%–87% of affected adults (4,5,7). Wilkens et al (8) found that superficial drusen were more commonly associated with visual field defects than deep

Address correspondence to Anna L. Silverman, BA, Department of Ophthalmology, Hamilton Glaucoma Center, University of California, San Diego, 9500 Gilman Drive, La Jolla, CA 92093-0946; anna.l.silverman@gmail.com.

drusen. The mechanism of drusen-related visual field loss is poorly understood. ONHD typically enlarge slowly throughout life and a slow progression of visual field loss is common (4,5,7). In rare cases, acute decreases in vision can occur due to vascular occlusion (9).

Recent advances in ocular imaging have improved our ability to image ONHD and have provided a means to obtain objective, quantitative measurements of ONHD and neighboring structures, including the retinal nerve fiber layer (RNFL) (5,10). Better in vivo imaging has the potential to improve our understanding of the pathogenesis of drusen-related visual field damage. The purpose of this review was to describe the use of 2 new optical coherence tomography (OCT) methods, enhanced depth imaging optical coherence tomography (EDI-OCT) and swept source optical coherence tomography (SS-OCT), and to evaluate their application in the assessment of ONHD.

CURRENT UNDERSTANDING

Prevalence of ONHD

Clinically recognized ONHD are estimated to occur in 0.3% of the population, with both genders affected equally. However, an autopsy series found a higher prevalence of 2.4% (11,12). The discrepancy between the clinical and autopsy findings is likely due to a high prevalence of undiagnosed drusen (4,5). ONHD are usually asymptomatic and therefore tend to present incidentally, either following routine ophthalmoscopy or following detection of an abnormality on visual field testing (13,14). In approximately 75% of individuals, drusen are bilateral, with a higher preponderance in the nasal rather than temporal optic disc sectors (4,15). ONHD appear to vary in prevalence among those of different racial backgrounds, with ONHD less common in those of African and Asian descent compared to other ethnic backgrounds (16,17). ONHD are more common in conjunction with systemic and ocular diseases, such as retinitis pigmentosa, pseudoxanthoma elasticum, and Alagille syndrome (5); yet the majority of patients have no predisposing ocular or systemic conditions (13,14).

Diagnosis

When superficial ONHD are present, they are often detected on ophthalmoscopy. If drusen are located deep in the optic nerve head (ONH), they may not be directly visible or may be confused with disc swelling due to papilledema, ischemic optic neuropathy, or other neurological conditions. Care must be taken to avoid overlooking genuine neurologic conditions, but in most cases, careful examination and supplementary imaging can readily differentiate these disorders and avoid unnecessary neurological investigations (4). The use of imaging devices to differentiate ONHD and papilledema is specifically discussed later in this review.

Etiology

Even though the first histopathological account of ONHD was more than 150 years ago, the mechanism underlying drusen formation is yet to be fully elucidated (4,18,19). It has been proposed that disc drusen might arise as a consequence of abnormal axonal metabolism leading to the deposition of calcium crystals in mitochondria, disruption of axons, and

extrusion of mitochondria into the extracellular space with further accumulation of calcified cellular contents (20). There is some support for this concept from histological findings. For example, following surgical excision of a druse, Kapur et al (21) found it to be composed of calcium phosphate [$Ca_3(PO_4)_2$], which has been observed to be a trigger for cell death.

Congenital anomalies of the ONH have been suggested as possible contributory factors. It has been proposed that the presence of a small scleral canal could lead to interruption of axoplasmic transport and ischemic changes (22), with resultant phosphate-dependent calcification of intracellular neural mitochondria and accompanying extracellular calcium accumulation (21). Nerve fiber degeneration and accumulation of calcified intracellular contents may also occur due to reduced axoplasmic flow secondary to a congenital anomaly of the ONH (23). An increased prevalence of ONHD has been observed in those with a family history, suggesting that ONHD, or an anatomical predisposition to drusen, might be inherited (22).

ONHD-Induced Visual Field Defects

Although disc drusen are usually asymptomatic, they frequently are associated with visual field defects (4,5,7). It is hypothesized that drusen-related visual field loss may occur as a result of mechanical stress on delicate structures within the prelaminar scleral canal (3). In addition, drusen may compress neighboring retinal ganglion cell axons, resulting in retrograde axonal degradation and further ganglion cell death (7). The visual field defects seen in ONHD range from an enlarged blind spot to defects similar to that seen with glaucomatous optic neuropathy (24,25).

Vascular Complications in ONHD

Congestion of the optic disc secondary to ONHD may lead to impaired blood flow and predispose to acute vascular events, such as retinal vein occlusion, retinal artery occlusion, and anterior ischemic optic neuropathy (3). In rare cases, dramatic visual field loss can occur due to vascular complications. In addition, chronic ischemia in parapapillary tissues can result in subretinal neovascularization, even in younger patients (3). Severe visual field loss has also been reported in eyes without evidence of an acute vascular event (4).

ONHD Progression

The size and relative location of ONHD may change over time, as evident from the change from deep buried drusen typical of childhood to the more visible superficial drusen of older age. Visual field defects may also progress, with an age-related increase in both frequency and severity of drusen-related field loss (26,27). Lee and Zimmerman (9) reported a 1.6% per year increase in severity of drusen-related field loss during a 36-month period. Both the location and size of drusen within the optic disc may impact the risk of visual field defect (2,4). It is notable that the relationship between disc drusen and defects of the RNFL and visual field has not been well documented, perhaps due to the limitations of previous imaging technology.

ESTABLISHED IMAGING TECHNIQUES

In addition to ophthalmoscopy, established imaging tests that have been useful for the detection of ONHD include B-scan ultrasonography, fundus autofluorescence (FAF), and spectral domain optical coherence tomography (SD-OCT). Fundus fluorescein angiography has also been used with drusen demonstrating irregular hyperfluorescence during the late frames. B-scan ultrasonography and FAF rely respectively on the hyperechoic and autofluorescent properties of the calcific drusen. We briefly discuss each of these technologies.

B-Scan Ultrasonography

Using B-scan ultrasonography, disc drusen appear as highly reflective round structures that can also be identified by their acoustic shadowing (Figs. 1, 2). B-scan imaging also may reveal additional calcium deposits invisible on ophthalmoscopy (28) and has been found to have good ability to differentiate ONHD and optic disc adema, with superior accuracy compared to modalities, such as FAF and computed tomography (CT) (29). B-scan is fast, relatively inexpensive, and practical enough for use even in children who are unable to sit still for long periods. Ultrasonography also provides some detail regarding the posterior limit of drusen and drusen dimensions; however, it has a relatively poor resolution and provides little information regarding the structural integrity of the neural retina.

Fundus Autofluorescence

FAF makes use of the inherent autofluorescent properties of ONHD. Autofluorescence occurs in macular degeneration due to the natural fluorophores, particularly lipofuscin, within the retinal pigment epithelium. The specific autofluorescent component(s) of disc drusen are not known (12). FAF can be performed using a standard fundus camera with appropriate filters or using a confocal scanning laser ophthalmoscope (cSLO) (Figs. 1, 2). FAF is useful for differentiating ONHD from optic disc adema (30). However, a major disadvantage of FAF is that it performs poorly in detection of deeper, buried drusen (4,31–33).

Fluorescein Angiography

Fluorescein angiography (FA) uses a fluorescent dye and camera to capture information regarding retinal and choroidal circulation. Pineles and Arnold (34) reported that FA can be used to reliably differentiate between ONHD and optic disc edema, even in cases where drusen were buried. A key characteristic of optic disc edema was the presence of diffuse, early fluorescein leakage. Buried optic disc drusen were evident by late peripapillary staining, which could be circumferential (80%) or nodular (20%). In addition, FA was useful in diagnosing coexisting disc edema and ONHD. But FA is an invasive procedure, and therefore, in cases of diagnostic uncertainty, effective non-invasive alternatives would be preferable.

Optical Coherence Tomography

SD-OCT may be used to image ONHD (35), providing high-resolution images compared to techniques such as B-scan ultrasonography and allows measurement of retinal layers,

including the RNFL (4,36,37). SD-OCT may be useful for distinguishing between buried ONHD and optic disc edema (29,38). Using SD-OCT, both ONHD and disc edema typically result in elevation of the ONH; the internal optic nerve contour is smooth in cases of disc edema but irregular in cases of ONHD (29). In a study of 92 patients, SD-OCT was able distinguish 45 patients with ONHD from 15 with disc edema and 35 controls (8). It was also noted in this study that RNFL thinning in patients with ONHD was particularly prevalent in the inferonasal and nasal areas (8). Savini et al (39) suggested that a structure known as the subretinal hyporeflective space (SHYPS), which is located between the retinal pigment epithelium and the choriocapillaris may be useful for differentiating ONHD and disc edema. Using OCT, it has been reported that SHYPS thickness is greater in eyes with disc edema compared to those with ONHD (36). SHYPS thickness greater than 464 μm had 85% sensitivity and 60% specificity in distinguishing between the 2 pathologies (36).

Although SD-OCT has shown promise as a tool for detection and diagnosis of ONHD, a disadvantage of conventional OCT technology is that as depth increases, the resolution of SD-OCT decreases, meaning deeper disc drusen are often poorly demarcated (10,35) (Table 1). Imaging the posterior limits of drusen is also difficult due to the hyperreflective anterior surface causing shadowing (5).

NEW IMAGING TECHNIQUES

Enhanced Depth OCT

EDI-OCT was first reported in 2008 by Spaide et al (40) to address the limitations of conventional SD-OCT for imaging deep ocular structures. The method initially described involved placing the OCT apparatus close enough to the eye to create an inverted view of the fundus (40,41). This places the coherence gate at a deeper plane than its usual position in the vitreous and moves the position of peak sensitivity from near the posterior vitreous in conventional OCT to the inner sclera for EDI-OCT (41). In EDI-OCT, the deeper layers are closer to the zero delay, with the result that these structures have a smaller frequency and lower shift. Using EDI-OCT it is possible to visualize structures 500–800 μm deeper than with conventional OCT.

EDI-OCT has been used to examine the choroid (40), but recently, its application for imaging ONHD has been explored (5,10). Sato et al (5) demonstrated that EDI-OCT had a high ability to detect ONHD, obtaining images of the posterior limits of disc drusen and measuring drusen area. Figure 3 shows an EDI-OCT image of a large optic disc druse. The circumference of the druse is clearly visible, which allows the cross-sectional area of the druse to be calculated. Druse volume could also be calculated from the complete volume scan.

EDI-OCT provides more information regarding the extent of disc drusen than FFA or B-scan ultrasonography. In a prospective comparative cross-sectional study, Merchant et al (10) found that EDI-OCT was able to detect ONHD more frequently than B-scan ultrasonography. When disc drusen were visible on dilated optic disc photographs or stereo-photographs, both EDI-OCT and B-scan ultrasonography identified the ONHD. However, in 25 eyes with suspected ONHD, EDI-OCT detected drusen in 17 eyes compared to B-scan

which detected drusen in only 7 eyes. Drusen were evident either as signal poor regions surrounded by short hyperreflective bands or as isolated or clustered hyperreflective bands without a signal poor core.

A further advantage of EDI-OCT is that it provides greater ability to assess the shape and structure of the drusen, which may have implications for visual function. EDI-OCT has proved useful for investigating the relationship between drusen and RNFL. Using EDI-OCT, Sato et al (5) found significant negative correlation between the diameter of disc drusen and the global RNFL thickness ($r = -0.61$, $P = 0.001$). In addition, there was a significant positive correlation between the disc drusen diameter and the number of sectors of thinned RNFL. Increased presence of drusen within the optic canal was also associated with thinner RNFL (5). It has been proposed that EDI-OCT might also be able to detect early drusen formation, which may be indicated by the presence of deep hyperreflective bands within the ONH (10).

EDI-OCT may also be used in conjunction with cSLO FAF to allow precise localization of the EDI-OCT scan to the region of interest (Figs. 1, 3).

Swept Source OCT

SS-OCT such as the deep range imaging OCT (Topcon, Tokyo, Japan) has been introduced recently with several modifications compared to conventional SD-OCT. SS-OCT uses a laser that sweeps across a range of wavelengths to produce an image in almost real-time with a scanning speed of 100,000 Hz at the 1 μm wavelength region (41,42). Despite differences in light source and detection methods, SS-OCT acquisition times are fast since the detector is much simpler (41). Deeper penetration of ocular tissue is achieved by using light of a longer wavelength, which is less affected by light scattering by the photoreceptors and retinal pigment epithelium. The SS-OCT light source has a center wavelength of 1,050 nm, yielding approximately 8 μm axial resolution (42).

SS-OCT has been shown to significantly improve visualization of the posterior ocular structures compared to conventional OCT (43). Similar to EDI-OCT, the advantage of SS-OCT in ONHD imaging is its ability to image the complete cross-sectional area of the druse. SS-OCT provides improved resolution compared to previous imaging methodologies, such as B-scan ultrasonography. SS-OCT also provides a wide 12.0 × 9.0 mm RNFL thickness map that allows evaluation of drusen-associated RNFL thinning. Being a new technology, there are few studies evaluating the use of SS-OCT for ONHD. Sato et al (5) used SS-OCT to image 4 eyes with ONHD and demonstrated that drusen were visible as ovoid regions of low reflectivity with hyperreflective curvilinear borders (Fig. 4).

CONCLUSIONS

New imaging technologies, such as EDI-OCT and SS-OCT, provide a means to quantify optic disc drusen dimensions and examine the integrity of neighboring structures in the retina and optic disc. These devices therefore provide the potential to develop better understanding of the relationships between disc drusen, RNFL loss, and visual field defects. They also provide a means to allow longitudinal assessment of drusen and may help explain

disease mechanisms. Further research using EDI-OCT and SS-OCT may identify risk factors associated with drusen-related visual field loss and help provide prognostic information. Although there are presently no known treatments for drusen-related field loss, improved understanding of the mechanism of neuronal damage through enhanced imaging may lead to developments in this area (44).

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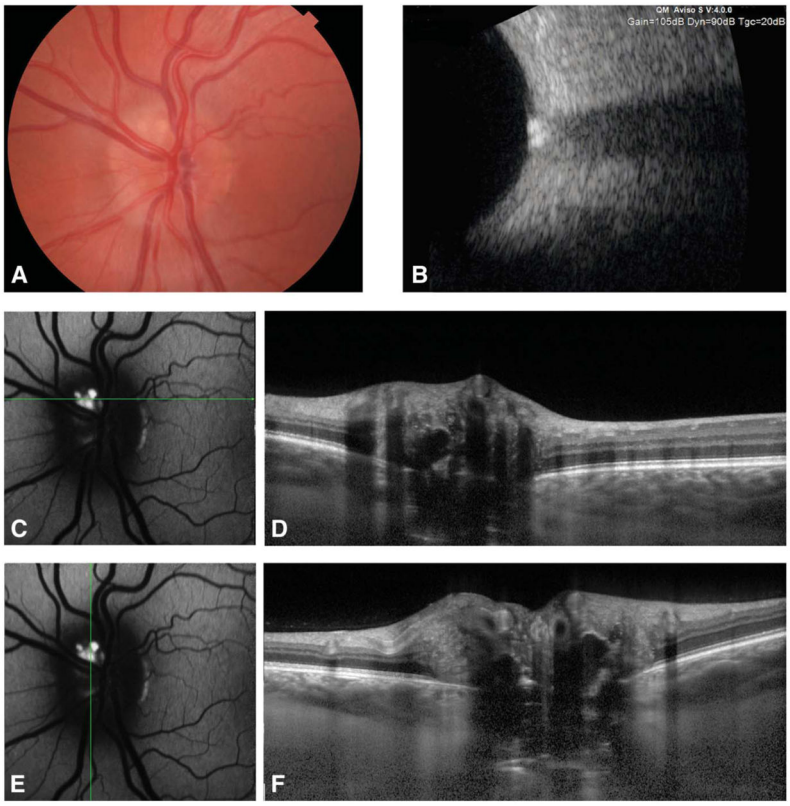

FIG. 1.

Fundus photograph (**A**), B-scan ultrasound (**B**), fundus autofluorescence images (**C**, **E**) and enhanced depth imaging optical coherence tomography (EDI-OCT) images (**D**, **F**) of left eye of subject with optic nerve head drusen. The green lines shown in the red-free images indicate the direction of the respective EDI-OCT line scans.

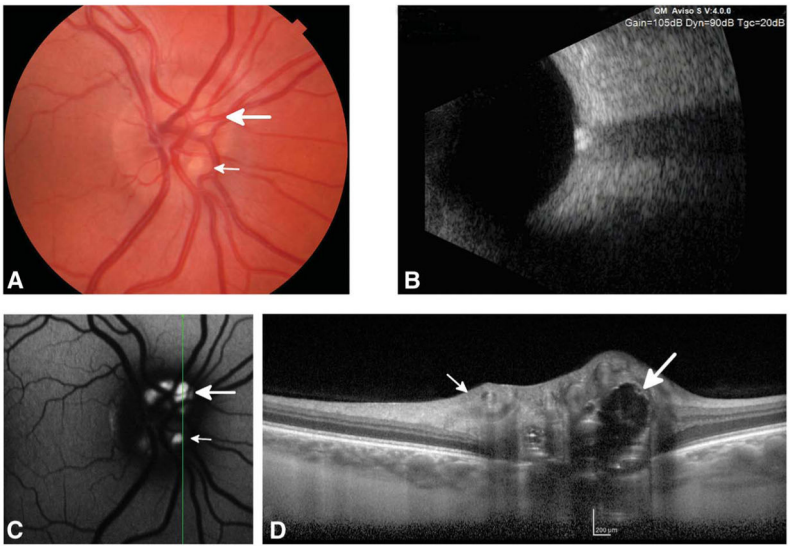

FIG. 2.

Fundus photograph (**A**), B-scan ultrasound (**B**), fundus autofluorescence images (**C**) and enhanced depth imaging optical coherence tomography (EDI-OCT) (**D**) of the left eye of subject with optic nerve head drusen. The green line in the red-free image indicates the direction of the EDI-OCT line scan. Superficial (*small arrows*) and buried drusen (*large arrows*) are shown.

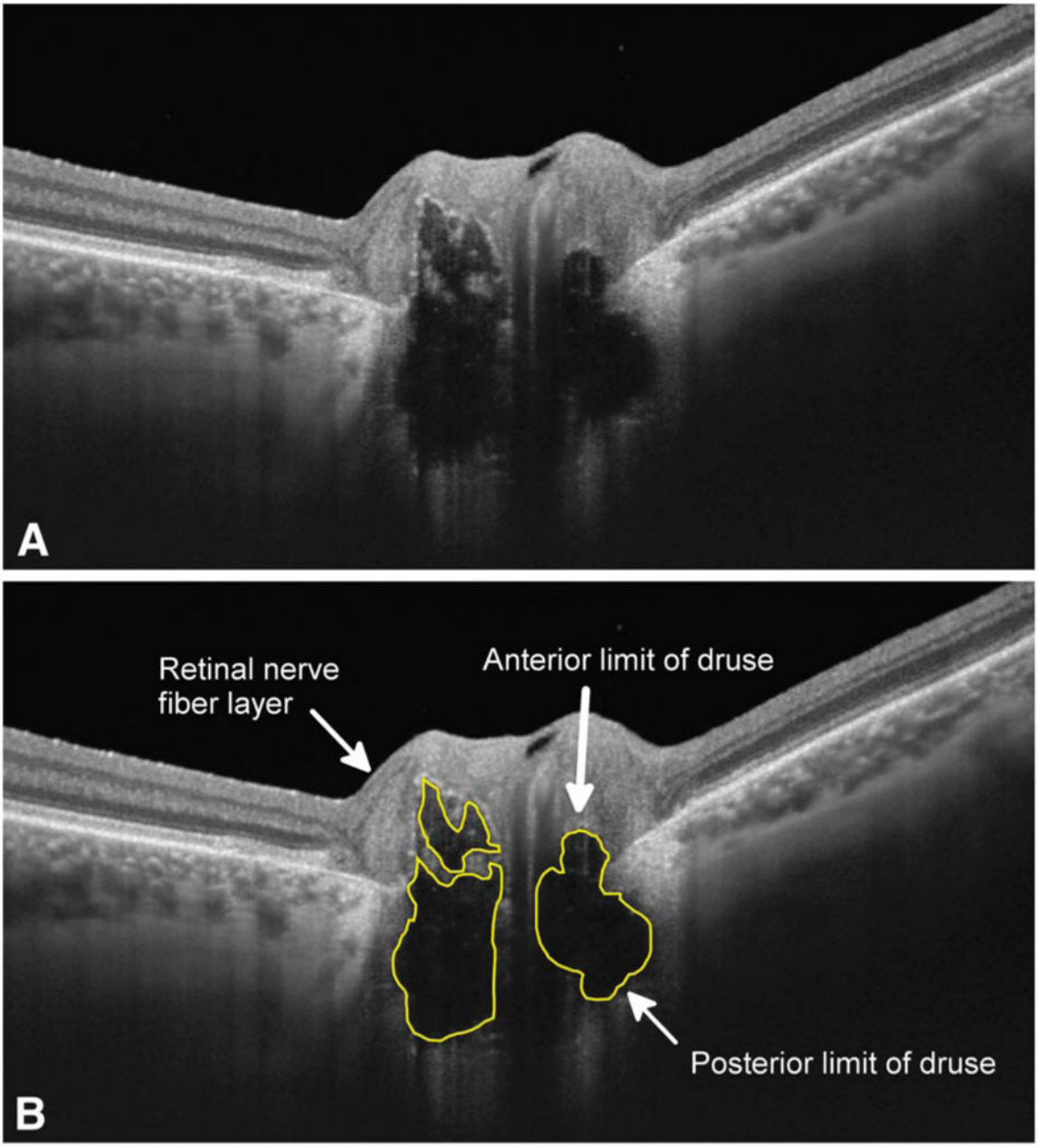

FIG. 3.

Enhanced depth imaging optical coherence tomography images of left eye of a subject with optic nerve head drusen (**A**), with the borders of the drusen outlined in yellow (**B**).

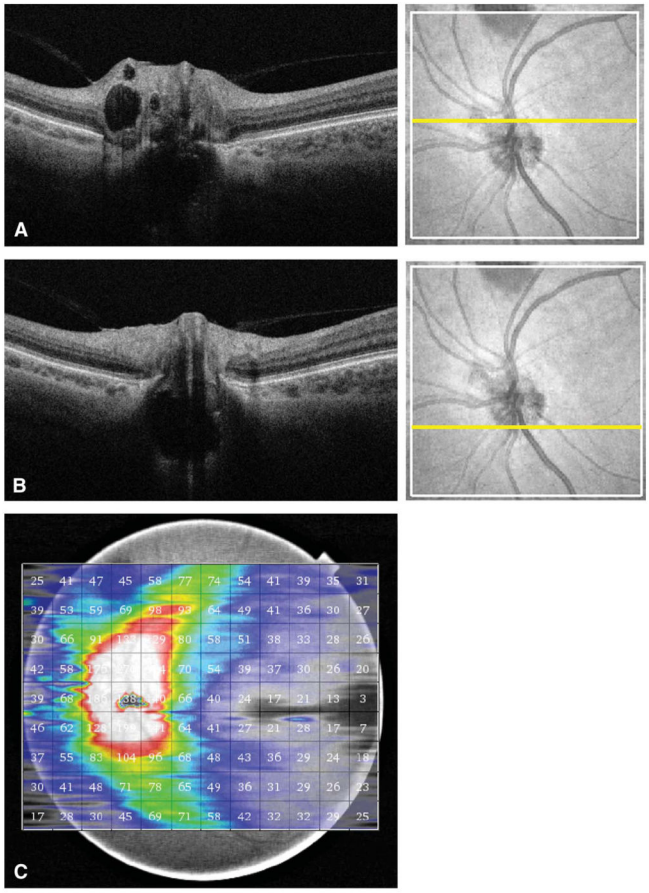

FIG. 4.

Swept source optical coherence tomography of the left eye of a subject with optic nerve head drusen (**A**, **B**). The yellow lines on the red-free images indicate the direction of the enhanced depth imaging optical coherence tomography. The corresponding retinal nerve fiber layer thickness “heat-map” is shown (lower image) (**C**).

TABLE 1

Comparison of strengths and weaknesses of imaging modalities for the detection of optic nerve head drusen

Imaging Modality	Strengths	Weaknesses
B-scan ultrasonography	Able to image deep drusen	Poor resolution
	Noninvasive	No information regarding retinal nerve fiber integrity
Fundus autofluorescence	Requires only a standard fundus camera with filters	Limited ability to detect deeper buried drusen
	Noninvasive	No 3-dimensional images
Fluorescein angiography	Able to differentiate between ONHD and optic disc adema	Invasive Small risk of serious allergic reaction
SD-OCT	Relatively easy to operate	Resolution decreases as depth increases
	High resolution	Unable to visualize posterior limits of drusen
	Able to differentiate between ONHD and optic disc adema	
	Quantitative assessment of retinal nerve fiber layer	
EDI-OCT and SS-OCT	Able to image the posterior limits and shape of optic disc drusen	SS-OCT is not yet widely available, whereas EDI-OCT can be performed using modified SD-OCT
	Relatively easy to operate	
	High resolution	
	Quantitative assessment of retinal nerve fiber layer	

EDI-OCT, enhanced depth imaging optical coherence tomography; ONHD, optic nerve head drusen; SD-OCT, spectral domain optical coherence tomography; SS-OCT, swept source optical coherence tomography.