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Imaging of Optic Nerve Head Drusen: Improvements with Spectral Domain Optical Coherence Tomography

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Abstract

Objective—To demonstrate a new algorithm that can determine the shape, location, and volume of optic nerve head drusen (ONHD) which were imaged with spectral domain optical coherence tomography (SDOCT).

Methods—One exenteration patient and four glaucoma patients with bilateral ONHD were recruited from the Massachusetts Eye and Ear Infirmary and from a private practice office. Images were obtained using an experimental SDOCT system developed at the Wellman Center for Photomedicine, Massachusetts General Hospital. With axial resolutions of about 6 μm, SDOCT can obtain 2-dimensional images in 1/29 of a second, compared to commercially available time domain OCT instruments with 10 μm resolution images in 1.28 seconds. The volumes of ONHD were calculated with a new algorithm and were then correlated with visual field mean deviation.

Results—SDOCT can display two-dimensional images comparable to histology as well as 3-dimensional videos of ONHD. ONHD are signal-poor regions with high-signal borders. Larger ONHD volumes are directly correlated with larger mean deviation absolute values on Humphrey visual field testing.

Conclusions—SDOCT is a potentially better technique for ONHD imaging and may improve the diagnosis and management of patients with both ONHD and glaucoma.

Keywords

optic nerve head drusen (ONHD); spectral domain optical coherence tomography (SDOCT); histology; glaucoma; imaging

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Introduction

Optic nerve head drusen (ONHD) are laminated calcified hyaline bodies.^{1,2} Clinically, they appear as globular bodies that protrude from the disc and therefore may obscure the disc margin.³ The reported incidence is 3.4 to 4.9 per 1,000 individuals in clinical studies,⁴ but a higher incidence of 20.4 per 1,000 individuals has been reported in autopsy studies.⁵

Although the exact mechanism for drusen formation has not yet been established, factors possibly involved in the pathogenesis include a small scleral canal, a congenitally dysplastic disc, abnormal vasculature, and altered axoplasmic transport.^{1,6–10}

Although many patients are asymptomatic, there are numerous reports of progressive visual field loss from optic nerve drusen.^{2,4,7,8} For example, ONHD has been associated with vascular anomalies such as abnormal branching of retinal vessels, a higher incidence of cilioretinal arteries, and retino-choroidal collaterals. These anomalies may somehow contribute to serious complications such as anterior ischemic optic neuropathy, central retinal vein or artery occlusions, subretinal neovascularization, and retinal hemorrhage.^{7–10} Acute vision loss resulting in total blindness has also been reported with ONHD.¹¹

Clinical dilemmas occur particularly in patients with co-existing physiologic cupping or glaucoma. For example, buried ONHD may obscure a physiologic cup, making assessment of the cup-disc ratio difficult. Assessment of the optic nerve in glaucoma patients with ONHD can be very difficult.^{7,12} Optic nerve head drusen per se can also cause any number of visual field defects such as a nasal step, an arcuate scotoma, enlargement of the blind spot, and generalized constriction.^{2,7} Accurate evaluation of optic nerve head drusen is also clinically important, because buried ONHD may be confused with disc edema. Treatment dilemmas may occur in patients with progressive visual field loss and co-existing ONHD and glaucoma. In these cases and despite current imaging modalities, it is difficult to tell whether progressive field loss is from the ONHD or the glaucoma.

There are many methods to diagnose ONHD. These methods have included direct visualization with ophthalmoscopy, autofluorescence before fluorescein angiography, ultrasonography, and CT scanning. Among those methods, B-scan ultrasonography has proven the most sensitive and useful.^{13,14} All of these techniques, however, can only assess if ONHD are present or not; however there is little or no information on the exact shape, size or location of the drusen. Although time domain optical coherence tomography (OCT; StratusOCT, Carl Zeiss Meditec, Dublin, CA) studies have shown not only retinal nerve fiber layer (RNFL) thinning but also documentation of scleral canal size in ONHD patients,^{7,8,10,15,16} this imaging modality still can not determine exact ONHD size, shape or location, which would be useful when trying to determine if progressive visual field loss is from ONHD or glaucoma.

Spectral domain optical coherence tomography (SDOCT) is a newer technology which enables unprecedented simultaneous ultra-high speed ultra-high resolution ophthalmic imaging.^{17–19} In addition to improved potential for the evaluation of various retinal diseases,²⁰ we believe that SDOCT allows for improved evaluation of optic nerve head pathologies such as glaucoma and ONHD.

This study compares histology of ONHD with images produced by a prototype SDOCT machine. Visual field mean deviation is then correlated with ONHD volume, which can be determined by our novel algorithm which determines ONHD borders.

Materials and Methods

Massachusetts Eye and Ear Infirmary and Massachusetts General Hospital Institutional Review Board approvals were obtained. Informed consents were obtained from all patients and were in accordance with the Health Insurance Portability and Accountability Act. Patient volunteers were recruited from a private practice office and from the Massachusetts Eye and Ear Infirmary Oculoplastics, Otolaryngology, and Glaucoma Services.

Patients with ONHD were recruited for this study. Exclusion criteria included patients with occludable angles or contraindications for dilation. For all patients, eyes had standard fundus photography [Topcon TRC 50IX fundus camera (Topcon, Tokyo, Japan) or Visucam Pro NM (Carl Zeiss Meditec, Dublin, CA)] and then imaging with the prototype SDOCT system which is described below. Other than case A, who would not agree to visual field testing, all patients did visual field testing using the SITA-standard 24-2 program of the Humphrey visual field analyzer 750i (Carl Zeiss Meditec, Dublin, CA).

Histology studies were possible in one patient (case A), because she was diagnosed with malignant melanoma with right orbital invasion that required exenteration surgery. A few hours before her exenteration surgery, she had fundus photography and imaging studies (i.e. OCT3 and SDOCT imaging) of her right eye. The exenterated tissue was initially placed into formaldehyde. A pars plana incision parallel to the limbus was made for 180 degrees in order to better allow the formaldehyde to enter the eye. After the exenteration specimen was examined and processed for the patient's usual care, the globe was placed into Karnovsky's solution (2.5% glutaraldehyde and 2% formaldehyde). The eye was then sectioned to isolate the posterior pole region that included the optic nerve and fovea. After embedding with epon, one-micron sections were cut on a Leica Ultracut UCT (Leica microsystems, Wetzlar, Germany) and then stained with 1% toluidine blue in 1% borate buffer.

SDOCT images were obtained using an experimental SDOCT instrument that was developed at the Massachusetts General Hospital, Wellman Center for Photomedicine. The light source was a superluminescent diode (SLD, Superlum, Russia) with a full width at half maximum spectral width of 50 nm centered at 840 nm (Figure 1). The low coherence near infrared light from the SLD light source is split to go to a reference mirror and to the retina, 80% and 20% respectively (Figure 1). As the light comes back from the mirror and the eye, it creates an interference pattern. This information is then analyzed by a spectrometer. After using Fourier transformation, an image is created.

The incident optical power into the eye was within American National Standards Institute standards.²¹ More detailed descriptions of the setup have been published previously.^{18–19}

After obtaining the SDOCT data, 3-dimensional (3D) SDOCT images of the optic nerve head and drusen were created using commercially available software from Amira™ (Mercury Computer Systems Inc., Chelmsford, MS, USA) interfaced with open-source C++ algorithms available from Insight Registration and Segmentation Toolkit (ITK). The 3D dataset was preprocessed with a gradient anisotropic diffusion filter in order to reduce noise while preserving the edges of prominent structures. The drusen were segmented on each 2-dimensional (2D) frame independently in order to identify the distinct edges. Finally, 3D reconstruction of the retinal surface topography and drusen segmentation was achieved by interpolating the segmentation between each 2D frame to define all points in 3D, followed by displaying the topography.

Results

Nine eyes of 5 patients were imaged. They were 3 female and 2 male patients with an average age of 58.8 ± 12.4 years. All patients were Caucasian. Patient demographics are summarized in Table 1.

For case A (Figures 2 through 4), prominent ONHD are seen at the superior nasal border of the optic nerve head OD (Figure 2A). The StratusOCT scan OD shows an elevated optic nerve head with a signal poor region below the surface (Figure 2B, arrow). Histology OD (Figure 3) shows a multilobulated large ONHD (asterisk) and smaller ONHD (arrows) above the lamina cribrosa and within the nasal side of the optic nerve head. The retina was detached during the tissue processing, and most of the calcific substance was lost. In Figure 4A, the single frame SDOCT image of patient A shows presumed drusen as signal-poor regions (asterisks) with relatively high-signal borders (thin arrows). Blood vessels are seen as large circular structures (arrowheads) with modest shadowing effect. Reconstructed 3D SDOCT images (Figures 4B, C) show the size, shape and location of the ONHD in relation to the optic nerve head. The calculated volume of the ONHD is 0.0304 mm^3 . The SDOCT images and drusen algorithm (Figures 4A–C) show good correlation with histology, which confirms the superior nasal location of the ONHD.

Figure 5 displays the fundus photos, Humphrey visual fields and 3D reconstructed SDOCT images of Cases B, C, D, and E. The calculated volumes of the ONHD, excluding the patients who have other ocular diseases (i.e. history of scleral buckle surgery and epiretinal membranes) which can affect visual field defects, are summarized in Table 2.

The volume (mm^3) of ONHD correlates well with and is directly proportional to the magnitudes of the mean deviation (Figure 6). With linear regression analysis, the r^2 value is 0.97, with an r square value above 0.8 indicating “excellent” correlation.

Discussion

Since Huang et al first described the technology of optical coherence tomography (OCT) over 15 years ago,²² OCT has become a widely-used technology in ophthalmology.^{3,12,15,16,20} The leading current commercially available OCT machine (i.e. the StratusOCT) is based on time domain OCT (TD OCT) technology. SDOCT uses a high-speed spectrometer to process spectral interference fringes that are generated from light from the reference arm and from the different layers of the retina.^{18–20,23} SDOCT’s more efficient method of data acquisition allows for retinal scanning at a faster rate of 29,000 A-scans per second. In contrast to the lower resolution of the StratusOCT system of 10 microns, SDOCT can achieve superior axial resolutions of 2 to 6 microns, depending on the light source.

The current study shows a new SDOCT algorithm that can detect the existence, location, shape and volume of ONHD with excellent anatomic correlation with histology (Figures 3, 4). For the first time, this new SDOCT algorithm allows for high-resolution quantitative 3D imaging with analysis of ONHD shape, size, and location (Table 2, Figure 5). Although computed tomography (CT) scanning can produce 3D images, the 1.5 mm cuts are too large in interval to even adequately assess the optic nerve head, let alone any smaller-sized drusen within the optic nerve head.

Our study is consistent with the non-ophthalmic literature that describes the expected findings of calcific structures visualized with OCT technology. Intravascular optical coherence tomography has been used for visualization of the coronary artery.^{24,25} Yabushita and colleagues investigated intravascular OCT images of 357 atherosclerotic arterial segments obtained at autopsy and showed that calcific aortic plaques are signal poor regions with high-

signal delineated borders.²⁵ In Figure 2B, the time domain OCT3 scans can show ONHD as signal poor regions but the expected highly reflective borders are poorly seen anteriorly and not seen at all posteriorly. The expected highly reflective borders, both anteriorly and posteriorly, are more clearly seen with 2-dimensional SDOCT imaging (Figure 4A).

There are distinct clinical advantages of 3D SDOCT imaging of ONHD. When a patient with glaucoma has ONHD, visual field defects can progress from either the glaucoma or the ONHD.^{7,8,12} For glaucoma patients with buried ONHD, the exact cause of visual field progression is even more difficult to determine. In Table 2 and Figure 6, we show that ONHD volume can be directly correlated with the visual field mean deviation values. With linear regression analysis, correlations were excellent ($r^2 > 0.8$). The results of this paper show that ONHD can affect visual field defects significantly, although it may not contribute to all of the visual field defects.

Although autofluorescence and B-scan images have been classically used to confirm or detect the presence of ONHD, both techniques result in 2-dimensional images that can not determine the volume, shape or location of ONHD in 3-dimension. Three-dimensional reconstruction of ONHD using SDOCT algorithms would allow clinicians to better monitor ONHD volume and location longitudinally, and therefore better enable the clinician to determine if progressive visual field defects are due to glaucoma or ONHD (Figure 5). For example, if the location of visual field progression is not consistent with the location of non-enlarging ONHD, a physician may be more likely to more aggressively treat the glaucoma.

Visual field defects can often be qualitatively correlated with the SDOCT ONHD images. Because of the more superior location and shape of the ONHD in Case B (Figure 5, eye number 2), the visual field defects inferiorly are likely attributable to the ONHD. In the left eye of patient B and both eyes of patients D and E (Figures 5, eye numbers 3, 6–9), the large circumferential choking appearances of the ONHD appear consistent with the more severe visual field defects, which may also be partly attributable to glaucoma. For patient C, the small nasal ONHD (Figure 5) do not appear to be the cause of the nasal visual field defects, which may simply be an artifact.

Like time domain StratusOCT which can show thinning of the RNFL with ONHD,³ SDOCT may also be potentially useful for longitudinal monitoring of RNFL thinning with ONHD. SDOCT RNFL thickness maps are different than the StratusOCT RNFL circular scan,¹⁷ which can produce only interpolated retinal thickness data.

Since ONHD on OCT are seen as a hollow round structures, differentiating small ONHD from large blood vessels may be difficult with conventional time domain OCT which has lower axial resolutions of 10 microns (Figure 2B). In contrast, SDOCT can distinguish blood vessels from ONHD more easily because of its better delineation of blood vessel margins as well as their adjacent shadowing artifacts (Figure 4A). Also, the continuity of blood vessels can be seen in consecutive frames or in serial video images and movies, while the finite borders of ONHD are eventually seen to end in subsequent serial frames or videos.

With histologic correlation of ONHD, our study confirms that SDOCT can accurately image ONHD. SDOCT is a potentially better technique for ONHD imaging and may improve the diagnosis and management of patients with both ONHD and glaucoma.

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Figure 1.

The basic set-up of a spectral domain optical coherence tomography system. The light from the light source is split to go to a reference mirror and to the retina. As the light comes back from the mirror and the eye, it creates an interference pattern, which is analyzed by a spectrometer, and an image is created. SLD=superluminescent diode, Ti=titanium.

Figure 2.

Results of testing OD for a patient (Case A) with optic nerve head drusen (ONHD). A: Fundus photo OD. Prominent ONHD are seen at the superior nasal border of the optic nerve head OD. B: StratusOCT3 (Stratus Optical Coherence Tomography 3; Carl Zeiss Meditec, Dublin, CA). The StratusOCT scan OD shows an elevated optic nerve head with a signal poor region below the surface.

Figure 3. Histology (magnification X 50, Toluidine blue staining) of a patient with optic nerve head drusen (ONHD, Case A, right eye). Multilobulated large ONHD (asterisk) and small ONHD (arrows) above the lamina cribrosa are seen on the nasal side of the optic nerve head. There is an artifactual retinal detachment, and most of the calcific substance was lost during tissue processing.

Figure 4.

A: Spectral domain optical coherence tomography (SDOCT) image (Figure 4 A) of a patient with optic nerve head drusen (ONHD) OD (Case A) and 3-dimensional reconstruction of SDOCT images (Figure 4 B, C). The SDOCT image shows signal-poor regions (asterisks) with relatively high-signal borders of presumed drusen (arrows). Near the surface of the optic nerve head, large circular structures are visible, which were seen to continue through serial images, and are probable blood vessels (arrowheads). B: The retinal surface viewed superiorly. Through the transparent surface, ONHD (blue) are clearly seen at the nasal aspect of the optic nerve head. C: View from the level of the retinal surface shows the spatial relationship between

the optic disc and ONHD (blue). The light source was a superluminescent diode laser which achieved an axial resolution of 6 μm .

Figure 5. Data from Cases B through E who are patients with optic nerve head drusen and glaucoma OU. Fundus photography (first column), Humphrey visual field testing 24-2 (second column), spectral domain optical coherence tomography (SDOCT) images of drusen (blue) when viewed at the level of the retinal surface (third column) and superiorly through a transparent surface (fourth column). The light source of the SDOCT machine was a superluminescent diode laser which achieved an axial resolution of 6 μm .

Figure 6. Correlation between the volume (mm³) of the optic nerve head drusen (ONHD) and the magnitude (dB) of the mean deviation (MD) from Humphrey visual field testing. Excellent correlation is seen with linear regression analysis ($r^2=0.97$). The larger the volume of the ONHD, the larger the visual field defect (as expressed as the MD).

Patient demographics of study patients with optic nerve head drusen (ONHD). VA=best corrected visual acuity, F=female, M=male, HSK=herpes simplex keratitis, SB=scleral buckling.

Eye number	Case	Age	Sex	Eye	VA	Ocular or orbital diseases	Operation(s)
1	A	46	F	OD	20/30	orbital melanoma	exenteration
2	B	59	M	OD	20/40	HSK, glaucoma	
3				OS	20/30	s/p retinal detachment, glaucoma	SB with cryopexy
4	C	50	M	OD	20/20	glaucoma	
5				OS	20/25	glaucoma	
6	D	78	F	OD	20/60	OU epiretinal membrane, glaucoma	OU cataract extraction + trabeculectomy
7				OS	20/100		
8	E	61	F	OD	20/25	glaucoma	
9				OS	20/30	glaucoma	

Table 2

The calculated volumes of optic nerve head drusen (ONHD) are shown with visual field parameters of enrolled patients who had ONHD and glaucoma OU but who did not have other diseases which can affect the visual field test (i.e. history of scleral buckle surgery and epiretinal membrane). MD=mean deviation.

Eye number	Case	Eye	MD (dB)	ONHD volume (mm ³)
2	B	OD	-8.65	0.201
4	C	OD	-3.4	0.0467
5	C	OS	-3.83	0.0675
8	E	OD	-23.49	0.648
9	E	OS	-24.28	0.839