Abnormal Foveal Morphology in Ocular Albinism Imaged With Spectral-Domain Optical Coherence Tomography

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Objectives: To evaluate the spectrum of foveal architecture in pediatric albinism and to assess the utility of spectral-domain optical coherence tomography (OCT) in ocular imaging of children with nystagmus.

Methods: Spectral-domain OCT imaging was performed on study subjects in 3 groups: subjects with ocular albinism (OA) or suspected OA with foveal hypoplasia, with nystagmus, and with or without iris transillumination; a subject with oculocutaneous albinism and Hermansky-Pudlak syndrome; and control subjects. Dense volumetric scans of each fovea were captured using standard and handheld spectral-domain OCT devices. Images were postprocessed and scored for the presence and configuration of each retinal layer across the fovea.

Results: High-quality spectral-domain OCT images obtained from each subject revealed a range of abnormalities in subjects with OA or suspected OA and the subject with oculocutaneous albinism and Hermansky-Pudlak syndrome: persistence of an abnormal, highly reflective band across the fovea, multiple inner retinal layers normally absent at the center of the fovea, and loss of the normally thickened photoreceptor nuclear layer at the fovea when compared with that in control subjects. The optic nerve was elevated in multiple eyes of subjects with OA or suspected OA and the subject with oculocutaneous albinism and Hermansky-Pudlak syndrome.

Conclusions: A spectrum of foveal morphological abnormalities is seen in subjects with OA or suspected OA, which in some cases contrasted with previous studies using time-domain OCT. These OCT findings clarify the morphology of foveal hypoplasia seen clinically. This imaging modality may be useful in evaluating children.

those with mutations in the tyrosinase gene that allow residual enzyme activity have OCA1B. Individuals have OCA2, OCA3, and OCA4 when there is a mutation in the P-gene on chromosome 15q, the tyrosine-related protein 1 gene, or the membrane-associated transporter gene, respectively.\textsuperscript{2}\textsuperscript{2} Hermansky-Pudlak syndrome (HPS), caused by mutations in 1 of 7 HPS genes, and Chédiak-Higashi syndrome, caused by a mutation in the lysosomal trafficking regulator gene, are multisystemic disorders associated with OCA.\textsuperscript{3} Except for OCA1A, individuals with the conditions described earlier may have some pigmentation in the skin, hair, and irides.

Optical coherence tomography (OCT) is the optical analogue to ultrasonography and measures the echo time delay and magnitude of reflected or backscattered light using low-coherence interferometry.\textsuperscript{11}\textsuperscript{11} Cross-sectional images are obtained by measuring the backscattered light while scanning across multiple sites in a transverse fashion. The data obtained are displayed as false-color or grayscale images.

A conventional time-domain (TD) OCT system (Stratus OCT; Carl Zeiss Meditec, Dublin, California) can provide 8- to 10-µm axial resolution and 512 axial scans in 1.3 seconds.\textsuperscript{11,12} Clinical limitations of the relatively slow standard TD-OCT are partially due to the subject’s eye motion, which can lead to image artifacts. Such artifacts may be reduced by exploiting cross-correlation algorithms that automatically align adjacent axial scans and with eye-tracking protocols.\textsuperscript{11}\textsuperscript{11} Ultrahigh-resolution OCT imaging with axial resolutions of 2 to 3 µm has been used to demonstrate retinal morphology with improved detail. Unfortunately, ultrahigh-resolution OCT is even slower than the TD systems, where scanning speeds are typically 150 to 250 axial scans per second.\textsuperscript{11}\textsuperscript{11} Thus, image artifacts due to eye motion are more severe and coverage is more restricted.\textsuperscript{11}

To overcome such limitations, ophthalmic imaging research is now progressively relying on the novel (Fourier) spectral-domain (SD) OCT systems.\textsuperscript{11,12}\textsuperscript{12} The SD-OCT systems have a higher speed and a sensitivity advantage over the conventional OCT systems (50 times faster than standard TD-OCT and 100 times faster than ultrahigh-resolution OCT imaging systems).\textsuperscript{11}\textsuperscript{11} Owing to the increase in speed, a single cross-sectional scan of 1000 A-scans can be captured, processed, and displayed in about 60 milliseconds. This reduces target motion artifacts, resulting in a more stable captured image. This is especially pertinent for the examination of young patients with known or suspected albinism, where the time of cooperative examination may be limited and nystagmus may affect scans acquired over a longer duration. More precise imaging of children with OA or suspected OA may give better insight into the range of morphological macular findings in the disease.

**METHODS**

The parents of study subjects consented to the subjects’ participation in a Duke University Institutional Review Board–approved study of SD-OCT imaging of the retina. The consent comprised investigator access to ophthalmic records, including other ophthalmic imaging studies performed at Duke University Eye Center. Study subjects were examined by a pediatric ophthalmologist (S.F.F.). Clinical examination included best-corrected visual acuity, presence and type of manifest nystagmus, skin color, hair color, iris color, and presence or absence of transillumination defects (assessed in a darkened room with the subject sitting at a slitlamp biomicroscope unless the child could not sit at the table-mounted slitlamp biomicroscope, in which case a portable slitlamp was used). Fundus examination was performed with an indirect ophthalmoscope and either a 20-diopter (D) or 28-D condensing lens. Skin biopsy and/or genetic testing were not performed in subjects with OA or suspected OA or control subjects in this study. The subject with OCA and HPS was diagnosed previously by genetic testing. Subjects with foveal hypoplasia (determined clinically via visualization with indirect ophthalmoscopy using a 20-D lens, looking for absence of the foveal pit), with nystagmus on clinical examination, and with or without iris transillumination defects were included in the group with OA or suspected OA. Control subjects were white, were aged between 5 and 11 years, had normal skin and hair pigmentation, had 20/20 visual acuity in each eye, and lacked nystagmus. The subject with OCA had a diagnosis of HPS. This subject was chosen as a positive control to verify the findings of OCA when compared with the subjects with suspected OA who did not clearly have albinism. As the subject with OCA and HPS was already scheduled to undergo anesthesia for strabismus surgery, imaging under anesthesia allowed for the entire posterior pole to be imaged under controlled conditions to ensure that the area where the fovea might be located would not be inadvertently bypassed during SD-OCT imaging.

The retinas of both eyes of the study subjects were then scanned using SD-OCT, and the eye with the best images, either right or left, was used for analysis. The subject with known OCA also had SD-OCT imaging of each retina performed while supine during scheduled anesthesia for strabismus surgery, and SD-OCT was performed using a portable, handheld, noncontact SD-OCT device (Bioptigen Inc, Research Triangle Park, North Carolina).

We used an SD-OCT system developed by one of us (J.A.I.) with operating software provided by Bioptigen Inc that was refined for imaging patients with OA (in collaboration with C.A.T.). The SD-OCT light source is a superluminescent diode (Superlum Diodes, Ltd, Carrigtwohill, County Cork, Ireland) with a central wavelength of 840 nm and a bandwidth of 49 nm, yielding a theoretical axial resolution of 6.3 µm in air and 4.6 µm in tissue. The lateral resolution of each A-scan was approximately 15 to 20 µm. The power incident on the study subject’s cornea was roughly 500 µW, which is well below the American National Standards Institute’s extended exposure limit of 750 µW for 8 hours.\textsuperscript{14}

In each eye, a retinal area of 10 × 10 mm or 12 × 12 mm was imaged in 5.8 seconds in a series of 100 horizontal SD-OCT scans containing 1000 A-scans in each B-scan. This produced 100 B-scans along the horizontal scan and spacing of 80 to 100 µm between scans. In addition to imaging the macula, the series of scans included the temporal border of the optic disc and the temporal arcades. In several eyes, 2 patterns of additional scans were captured: first, the scans followed the same sampling as earlier except that they were oriented 90° to the horizontal; second, a 5 × 5-mm area was imaged with 200 horizontal B-scans of 500 A-scans each, resulting in 25-µm spacing between scans. Each image set was captured in 5.8 seconds.

By collapsing SD-OCT B-scans (averaging all pixels) on an axial line, a 2-dimensional image analogous to a fundus image, called the summed voxel projection (SVP), is created.\textsuperscript{15,16} This technique allows for creating the landmark map useful to register a cross-sectional OCT image to the fundus...
RESULTS

Seven white study subjects (aged 4–13 years), 2 with OA and 5 with suspected OA, had retinal imaging of both eyes by SD-OCT. These study subjects had foveal hypoplasia on clinical examination, best-corrected visual acuities from 20/40 to 20/80 (0.30–0.60 logMAR; median, 0.48 logMAR), mild skin pigmentation, blue, green, or hazel irides, and nystagmus (Table 1). Five of the 7 subjects with OA or suspected OA did not have definite transillumination of the iris. Transillumination defects were recorded as absent only after careful examination using slitlamp microscopy in a darkened room before pupil dilation. Iris transillumination was not graded. Four white control subjects of similar age without OA were imaged for comparison. These study subjects had normal skin and hair pigmentation, pigmented irides, normal visual acuity, and no nystagmus. Additionally, the study subject aged 4 years with known OCA and HPS, 20/200 visual acuity (1.00 logMAR), little to no skin melanin pigment present, foveal hypoplasia, blue irides with prominent transillumination defects, and nystagmus was imaged. Demographics of study subjects are included in Table 1.

Table 2 summarizes the results of analysis of SD-OCT images of each subject. As shown in Figures 1, 2, 3, 4, and 5, imaging revealed a range of changes in the foveal architecture of eyes with OCA and those with OA when compared with control subjects. These included variable loss of normal foveal architecture present on SD-OCT images of the fovea and increased signal from the choroid and sclera. Optic nerve thickening was also observed on SD-OCT scans of 4 subjects with OA or suspected OA and the subject with OCA and HPS. Normal SD-OCT morphology included a sloping foveal depression, thickening of the hyporeflective photoreceptor nuclear layer at the fovea with bulging upward centrally within the fovea, and centripetal displacement of the nerve fiber layer, ganglion cell layer, inner plexiform layer, and outer plexiform layer with a broadening Henle fiber layer extending from the foveola (Figure 1). In control subjects, the choroidal vessels were minimally visible and the sclera was not imaged with SD-OCT.

The normal foveal depression was a clear hallmark of the fovea in the eyes of the control subjects (Figure 1). Although the control subjects showed subtle variation in the thickness of the inner retinal layers surrounding the fovea, they all demonstrated the normal centripetal distribution of cells extending out of the fovea. The normal displacement of these layers and the broadening of the Henle fiber layer out of the fovea were absent in every one of the eyes of the subjects with OA or suspected OA and the subject with OCA and HPS. In 1 eye from a subject with OA, a subtle depression of the retina was visible at the foveal site even though reflective bands consistent with inner retinal layers—including the nerve fiber layer—persisted across this site (subject 5) (Table 2). In another subject with sus-
Although conventional TD-OCT has shown single scans marks of the fovea on SD-OCT scanning of the macula, is associated with absence of all of the morphologic hallmarks of the fovea on SD-OCT scanning of the macula. In this study, we demonstrate that foveal hypoplasia in OCA (Table 2 and Figures 4 and 5) and moderately elevated in eyes of the single subject with OCA and HPS (subject 10) with loss of foveal contour,6,21 the high-resolution and 3-dimensional imaging achieved with SD-OCT handheld scanning of a subject during examination under anesthesia allows assured definition of the absence of foveal morphology. From 3-dimensional scan stacks, the inner retinal layers including the ganglion cell and nerve fiber layers are shown to definitely extend intact across the fovea without thinning. Similar unusual foveal abnormalities were found on examination of eyes of children with possible OA or OCA. These children, with visual acuities of 20/40 to 20/80 and mildly hypopigmented irides, demonstrated loss of foveal depression and persistence of inner retinal layers across the fovea. The normal centripetal displacement of inner retinal elements with the Henle fiber layer radiating out from the foveola was absent in all of these eyes. A few of these eyes in subjects with OA or suspected OA showed a slight suggestion of 1 or 2 elements of foveal development (Table 2); however, no eyes showed inner retinal layer displacement.

Comparing between the 2 affected groups, we found persisting ganglion cell nuclei and plexiform and inner nuclear layers in all of the subjects (in contrast to the control group). We also found that although the scale of foveal depression loss, nerve fiber layer thinning, and photoreceptor nuclear layer thinning varied among the subjects with OA or suspected OA, when the microarchitecture of the entire inner retina was considered, all of the eyes of subjects with suspected OA and the eye of the subject with OCA and HPS were clearly abnormal. In this small study group, we were unable to correlate visual acuity with the level of foveal development. The difficulty in using OCT technology to image children with known and suspected OA is movement on the part of the child, whether due to the nystagmus or short-
ened attention typical of young children. The rapid image acquisition of SD-OCT does not completely eliminate this challenge but improves resolution of each scan and allows more precise imaging even when faced with nystagmus. The rapid scanning also allows repeated imaging at a single location and results in higher-resolution summed scans (Figure 2). However, in children with nystagmus, it still may be difficult to be certain that the fovea is captured during an SD-OCT scan. Use of a handheld SD-OCT system allowed us to bring SD-OCT imaging into the examination under anesthesia and to capture definitive 3-dimensional images across the macula in a child with nystagmus (Figure 3).

The analysis in this study is based on SD-OCT imaging and is compared with previous TD-OCT studies, expanding on those findings. Some of our findings support many of those in previously published articles, including the persisting retinal layers across the fovea, although using SD-OCT allows better determination of which layers actually persist and affect overall image quality. Seo et al describe the characteristic TD-OCT findings of albinism as hyporeflectivity of the fovea, lack of foveal depression (which we also noted), and increased reflectivity from the choroidal layer. The hyporeflectivity of the photoreceptor layer of the...
fovea may have been due to limited image quality from the TD system or from the hyperreflectivity of the nerve fiber layer across the fovea. We did not find a difference in photoreceptor reflectivity in the subjects with OA or suspected OA or the subject with OCA and HPS. Seo and colleagues also describe a "tram track sign" caused by increased transillumination of the choroidal layer and increased reflectivity of the choroidal space. This was not seen in our study. We found increased visualization of the choroidal vessels and sclera in subjects with OA or suspected OA and the subject with OCA and HPS, with hyporeflectivity of the large choroidal vessels contrasting with the prominent hyperreflectivity of the underlying sclera. Reflectivity of a tissue layer on SD-OCT is a function of both the reflectivity of the structure and the shadowing or loss of signal from reflectivity of overlying structures. The absence of pigment in the retinal pigment epithelium and choroid in the subjects with OA or suspected OA and the subject with OCA and HPS results in a pronounced increase in signal (pertinent at the 830-nm central wavelength) extending into the choroid and sclera. Because of increased depth of scanning with this system compared with the TD system, what appeared as a tram track in the previous study is clearly hyperreflectivity from the retinal pigment epithelium on one side and the sclera beneath the hyporeflective choroidal vessels. In their observational case report of a 10-year-old girl with OCA who was imaged using OCT, Meyer et al23,24 also showed a lack of foveal depression. They reported increased foveal thickness greater than 300 µm in their patient with OCA compared with a 150-µm-thick fovea in a control eye. They speculated that the fovea was filled with hyperreflective tissue, possibly including multiple ganglion cell layers. In our study, we believe that the increased foveal thickness in subjects with OA or suspected OA and the subject with OCA and HPS is due to the persisting nerve fiber layer, ganglion cell layer, inner plexiform layer, inner nuclear layer, and outer plexiform

Figure 3. Summed voxel projection of a spectral-domain optical coherence tomographic 3-dimensional scan of a subject with oculocutaneous albinism (subject 10) (Table 2) (A) and the cross-sectional scans corresponding to the red dotted lines in part A (B) across the center of the presumed fovea and at several steps away from the fovea. There is high reflectivity across the fovea, suggesting a persisting nerve fiber layer. Multiple inner retinal layers, normally absent at the center of the fovea, persist across the fovea. The photoreceptor nuclear layer bulges upward at the fovea; the external limiting membrane, photoreceptor inner segment layer, and photoreceptor outer segment layer appear normal. The white dotted line in part A illustrates the position of the B-scan in Figure 4.

Figure 4. Cross-sectional scan at the optic nerve corresponding to the white dotted line in Figure 3A from the left eye of the subject with oculocutaneous albinism and Hermansky-Pudlak syndrome. Note the elevation of the optic nerve, which was seen in both eyes in this subject.
layer. In their observational case report of a 79-year-old man with foveal hypoplasia who was imaged using OCT, McGuire et al\textsuperscript{21} confirm some of our findings as they also found continuation of the outer nuclear layer, inner nuclear layer, and ganglion cell layer across the fovea. However, they describe a prominent photoreceptor layer centrally. In contrast, we found that the photoreceptor layer showed mild loss of thickness in SD-OCT scans across the abnormal site of the fovea in the subjects with OA or suspected OA and in the subject with OCA and HPS when compared with the normal thickening of the photoreceptor layer in the fovea of control eyes.

In using SD-OCT technology, the inner retinal layers persisting across the fovea and also the choroid and scleral reflectivities can be better defined in subjects with OA, suspected OA, and OCA. Evaluating how each layer contributes to the overall reflectivity and hyporeflectivity seen on high-resolution scanning provides a better overall picture of the anatomy of the hypoplastic fovea seen in OCA and OA or suspected OA. Albinism as a disease can vary from a total lack of melanin in all tissues and poor visual outcomes seen in some forms of OCA to mild hypopigmentation (or normal pigmentation in most tissues) and unimpaired visual acuity seen in albinoidism.\textsuperscript{7,25} For example, choroidal pigmentation was comparable to that in control subjects in 1 subject with OCA (subject 10) (Table 2). By comparing findings in control subjects with the extreme findings in OCA, a better understanding of changes at the retinal microarchitecture can be obtained. This imaging study based on tissue reflectance demonstrates morphology but cannot demonstrate the function of cellular elements in the retina.

Of note, we unexpectedly observed abnormal elevation of the optic nerve head in 4 of the 6 subjects with OA, possible OA, or OCA. We did not design the study to evaluate the optic nerve head and did not have images of the optic nerve in any of the control subjects. However, previous reports of OCT imaging of the nerve fiber layer at the optic nerve in healthy pediatric subjects\textsuperscript{26} and in pediatric subjects with ambiolipia\textsuperscript{22} showed no such elevation. The optic nerve thickening in subjects with OA or suspected OA and the subject with OCA and HPS could be a coincidental finding; however, this is an intriguing association in a disease with abnormal redirection of retinal axons further along the optic pathway at the chiasm. It is possible that in a very blond fundus where the optic nerve appears gray and its borders are more difficult to delineate, optic nerve head elevation could be present without being clinically appreciated. The optic nerve thickness will be evaluated prospectively in a future study.

It is important to correlate the SD-OCT findings in this study with known histopathological findings in eyes of subjects with OCA. Foveal hypoplasia was noted to be a characteristic in OCA in several histopathological studies in the early 20th century.\textsuperscript{28-32} Zhou et al\textsuperscript{35} describe the ocular findings in a patient with type 1 HPS. Hermansky-Pudlak syndrome has a triad of findings including OCA, platelet dysfunction, and ceroid lipofuscin accumulation. Zhou and colleagues describe a patient who had macular transparency, absence of foveal pits, and foveal light reflexes suggesting foveal hypoplasia, which was confirmed with TD-OCT. On pathology specimens, they describe abnormal melanocytes in ocular tissues, posterior embryotoxon, ciliary body hyalinization, foveal hypoplasia, marked hypopigmentation, and ocular hemorrhages. The study did not include any images of the fovea or any descriptions of the retinal layers at the presumed site of the fovea. They did note a lack of differentiation at the fovea and a retinal pigment epithelium with few melanin granules. In another article, Mietz et al\textsuperscript{39} describe an eye from a 99-year-old patient with complete OCA in which they were unable to find an area of foveal differentiation after serial sections through the posterior pole. They noted partial atrophy of the optic nerve head in a vertical hourglass configuration.

Imaging with SD-OCT gives the clinician much more detailed information regarding the retina in patients with OCA and in those with known or suspected OA. A grading schema similar to the one proposed by Seo et al\textsuperscript{14} could be implemented, one with greater definition based on the more exact details provided by high-speed, high-resolution SD-OCT imaging. Diagnostic signs of OA should be searched for in an adequate retinal OCT image set. It is very important for the clinician to recognize that analysis of an OCT image from outside the fovea could be misleading as the image could appear to represent foveal hypoplasia in an eye with a normal fovea (Figure 1B, scan 38 or 58). The following cardinal signs should be evaluated with:...
an adequate OCT image set: (1) absence of central foveal depression; (2) persistence of ganglion and plexiform (reflective) retinal layers across the fovea; and (3) persistence of the nerve fiber layer (although this is slightly less common than the other signs). A very prominent image of the entire choroid is also common in these subjects, although this may vary slightly depending on the level of choroidal pigmentation. Our study was limited by the inclusion of only 1 patient with known OCA. Study of SD-OCT in additional eyes of children with OCA could provide data corroborating our current findings. With the new data provided by this imaging technique, new questions arise regarding the pathophysiology of OA. Is it solely the lack of melanin production involved in this disease or is there another process causing the persistence of multiple retinal layers normally absent in the fovea? Is it the chiasmal misrouting seen in OA and OCA that leads to a retrograde effect on foveal development? As a new imaging modality easily applied to children even in the presence of nystagmus, SD-OCT may provide valuable structural detail in children with suspected foveal hypoplasia and albinism.

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Additional Information: Through their university, Drs Farsiu, Izzat, and Toth have filed a provisional patent application for fast detection and segmentation of drusen in retinal optical coherence tomography images. Dr Toth has filed a patent application for a method and system of coregistering optical coherence tomography with other clinical tests.

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