Published in final edited form as:

Am J Ophthalmol. 2012 May ; 153(5): 883–889.e2. doi:10.1016/j.ajo.2011.10.033.

Infrared Imaging and Optical Coherence Tomography Reveal Early-Stage Astrocytic Hamartomas Not Detectable by Fundoscopy

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Abstract

Purpose—To describe and correlate the features of astrocytic hamartomas using multimodal imaging.

Design—Prospective, non-comparative, observational case series.

Methods—This was a single-center study of 4 patients (8 eyes) with tuberous sclerosis complex. A complete ophthalmologic examination, fundus photography, fundus autofluorescence (FAF), infrared imaging, and spectral domain optical coherence tomography (SD-OCT) were performed for each patient. Images from each modality were analyzed and compared.

Results—In 2 patients, infrared imaging and SD-OCT detected occult retinal astrocytic hamartomas that were not observed on clinical examination or color fundus photography. FAF demonstrated the greatest contrast between lesions and surrounding retina but failed to identify one occult lesion that was detected with infrared imaging and SD-OCT. SD-OCT revealed lesions arising from the retinal nerve fiber layer with overlying vitreous adhesions, hyperreflective dots, and optically empty spaces at all depths of the tumor. Hamartomas were hyporeflective on infrared imaging and hypofluorescent on FAF. FAF of some lesions demonstrated hyperautofluorescent spots.

Conclusions—Infrared imaging and SD-OCT aid in the detection of astrocytic hamartomas that are not visible on clinical examination or color fundus photography. SD-OCT enhances visualization of structural details. FAF is a useful adjunctive test to obtain greater contrast between

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Financial Disclosures: none.

Author Contributions: Study design and conduct (LX, TRB, JPG, VBM, SHT); collection, management, analysis, and interpretation of data (LX, TRB, JPG, VBM, SHT); and preparation, review, or approval of the manuscript (LX, TRB, JPG, VBM, SHT).

Conformity with Author Information: This prospective study was approved by the Institutional Review Board of Columbia University and adhered to the tenets of the Declaration of Helsinki. All participants provided signed, informed assent and consent for participation in the study and for the publication of the data obtained.

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lesions and surrounding retina. The ability to monitor structural changes over time in astrocytic hamartomas using SD-OCT may be beneficial for monitoring the success of systemic chemotherapy in the treatment of various tuberous sclerosis tumors.

Keywords

astrocytic hamartoma; retina; scanning laser ophthalmoscope; autofluorescence; optical coherence tomography; tuberous sclerosis

Introduction

Tuberous sclerosis complex is an autosomal dominant disorder with an incidence of 1:10,000 to 1:25,000 births.^{1, 2} More than half of patients have retinal astrocytic hamartomas which are predominantly composed of well-differentiated glial astrocytes.^{1, 2} Astrocytic hamartomas are usually stable over time,^{1, 2} though a giant-cell variant has been reported and is associated with a more aggressive disease course.³

Ophthalmoscopically, retinal astrocytic hamartomas demonstrate considerable heterogeneity. Some lesions appear elevated and distinct from the surrounding normal retina,^{1, 2, 4} while others are more subtle with a color similar to the fundus background. Identifying these more subtle lesions is important during pediatric fundus examination, where identification of multiple retinal lesions can help in diagnosing tuberous sclerosis.^{5, 6} Therefore, imaging modalities that offer enhanced visualization of subtle lesions would be clinically useful. In this study, we compare the appearance of astrocytic hamartomas on fundus autofluorescence (FAF), infrared imaging, and spectral domain optical coherence tomography (SD-OCT) to fundus examination and photography.

Methods

Between October 2010 and January 2011, four patients with diagnosed tuberous sclerosis were examined at the Edward S. Harkness Eye Institute, Columbia University. Each patient underwent a complete ophthalmic examination, including measurements of best corrected visual acuity (BCVA), dilated ophthalmoscopy, and color fundus photography. FAF, infrared imaging, and SD-OCT of all patients was performed with the Spectralis confocal scanning laser ophthalmoscope (SLO)-OCT (Heidelberg Engineering, Heidelberg, Germany). This instrumentation allows for infrared or FAF scans to be obtained simultaneously with registered SD-OCT images. Standard methods of image acquisition were employed for all imaging modalities. To improve signal-to-noise ratio, each FAF image was composed of at least 9 single 30° × 30° images. Protocols for SD-OCT scans included 40 high-resolution frames per B-scan for volume scans and 100 high-resolution frames for 9 mm line scans. However, settings for resolution, the number of frames per B-scan, and the number of B-scans per volume scan were adjusted depending on patient cooperation and fixation.

Results

Four patients with tuberous sclerosis (2 males, 2 females) were examined. No patients reported a family history of tuberous sclerosis, and all patients were treated in the past with vigabatrin for infantile spasms refractive to other treatments. Their case histories are presented below.

Case 1

A 12-year-old Caucasian boy with BCVA of 20/25⁺¹ and 20/25⁻² presented with a large astrocytic hamartoma in the left eye. FAF and SD-OCT of this lesion demonstrated numerous hyperautofluorescent spots and hyperreflective dots, respectively. Infrared imaging and SD-OCT imaging of the right eye revealed a subtle retinal astrocytic hamartoma that was not visible on clinical exam or color fundus photography. FAF imaging failed to identify this lesion (Fig 1).

Case 2

A 13-year-old Caucasian boy presented with bilateral astrocytic hamartomas. BCVA was 20/20 bilaterally. Clinical examination of the right eye identified a lesion superficial to the inferior arcade and a more subtle lesion further inferotemporally. Infrared imaging and FAF offered enhanced visualization of the more subtle lesion (greater contrast compared to the retinal background). The SD-OCT scans of both eyes revealed hyperreflective dots and discrete hollow cavities (optically empty spaces) at varying depths of the tumors. The optically empty spaces co-localized with hyperautofluorescent spots seen in FAF (Fig 2).

Case 3

A 9-year-old Caucasian girl presented with bilateral astrocytic hamartomas. BCVA was 20/20⁻¹ and 20/25⁻². Clinical examination of the left eye revealed multiple lesions around the optic nerve and a subtle lesion over the inferotemporal arcade. Both FAF and infrared imaging allowed greater visualization of the subtle lesion. FAF also revealed two distinct areas of hypoautofluorescence around the optic nerve. SD-OCT revealed optically empty spaces at varying tumor depths in the left eye and hyperreflective dots in the lesion in the right eye (Fig 3).

Case 4

An 11-year-old Hispanic girl presented with an astrocytic hamartoma in the left eye. BCVA was 20/20⁻¹ and 20/30⁻¹. Clinical examination and color fundus images of the right eye revealed no obvious abnormality, but infrared imaging, FAF, and SD-OCT revealed an occult lesion in the superior macula. Following localization with infrared imaging, FAF, and SD-OCT, the lesion was retrospectively identified on the color photo as a very faint discoloration and slight obscuration of the vessel (Fig 4).

Discussion

We describe FAF, infrared imaging, and SD-OCT characteristics of retinal astrocytic hamartomas in a series of 4 patients with tuberous sclerosis. The yellow/gray color of a small retinal astrocytic hamartoma can be difficult to distinguish from the fundus background. In cases 1 and 4, infrared imaging and SD-OCT images demonstrated occult lesions that were not detected clinically. In case 1, even after its localization with infrared imaging and SD-OCT, the occult lesion was not detectable on color fundus photography or even on FAF (Fig 1, **left column**). In case 4, the occult hamartoma was clearly outlined by FAF, infrared imaging, and SD-OCT. After its localization, it was visualized on the color photo, albeit with difficulty (Fig 4, **left column**). In case 2 (Fig 2, **left column**) and case 3 (Fig 3, **right column**), FAF, infrared imaging, and SD-OCT rendered subtle lesions more easily identifiable.

In general, the extent of lesions was similar on FAF, infrared imaging, and SD-OCT (examples shown in Fig 4). However, our series found infrared imaging and SD-OCT to be the most sensitive imaging modalities to detect small lesions, as FAF failed to demonstrate the occult lesion in case 1 (Fig 1, **left column**). It may be that small lesions have insufficient

tissue mass to block the background FAF signal. However, FAF is useful in certain cases as an adjunctive test to provide images of astrocytic hamartomas with enhanced contrast compared to infrared imaging (Fig 4). Infrared imaging, however, was particularly helpful for topographical localization of smaller lesions, which were then imaged further with targeted SD-OCT scans. This avoided the need to perform dense SD-OCT scans of the entire posterior pole, which can be both difficult and impractical, especially with limited cooperation in children.

In a previous publication, Shields et al. described time-domain OCT findings of multifocal, round, confluent moth-eaten empty spaces with posterior shadowing in only the anterior third of astrocytic hamartomas.⁷ It was proposed that the empty spaces represented either foci of calcification or intratumoral cavities, as both calcification and cavities were found on histopathology.⁸ Using SD-OCT in this series, we visualized these spaces at all depths of the astrocytic hamartoma (Figs 2, 3), likely due to the superior resolution and enhanced tissue penetration provided by spectral domain, as opposed to time domain, technology. In case 2, we observed that these spaces co-localized with the dense hyperautofluorescent spots on FAF (Fig 2, **bottom row**). However, in the left eye of case 3, even though the moth-eaten empty spaces were present, hyperautofluorescent spots were not observed (Fig 3, **right column**). In addition, none of the optically empty spaces found in our series had posterior shadowing (Figs 1, 2, 3). Since calcium from optic nerve drusen shows significant posterior shadowing on SD-OCT,⁹ further histopathological assessment of the composition of the hyperautofluorescent material in astrocytic hamartomas is required.

One of the most striking new features that we observed was the presence of hyperreflective dots on SD-OCT (Figs 2, 3). Similar dots had been described on SD-OCT of occult choroidal neovascularization in eyes with age-related macular degeneration and were theorized to represent fibrovascular activity.¹⁰ Further histopathological study is needed to establish the exact source of these dots, but astrocytic hamartomas and other tuberous sclerosis lesions are known to be highly vascular tumors.^{11, 12} It would be interesting to see if lesions with more hyperreflective dots can be selectively targeted by anti-angiogenic medications in future research.

Furthermore, with clinical trials being performed for systemic tumor-shrinking agents such as rapamycin, changes in astrocytic hamartomas, as imaged by SD-OCT, may be used as a surrogate marker of systemic treatment efficacy. It is known from clinical observation that astrocytic hamartomas, when they do progress, do so in a slow fashion,^{1, 2} but no natural history study has quantified their changes over time. This is now possible with the “progression” mode on the Spectralis SLO-OCT, which sections the same region of retina at subsequent visits. Having a documented natural history would allow assessment of the progression (or regression) of retinal hamartomas in patients receiving systemic therapy. For this purpose, SD-OCT would have the advantages over magnetic resonance imaging (MRI) of being less expensive, quicker to perform, and providing higher resolution. Images also can often be obtained in young children without general anesthesia, which is typically required for an MRI.

In summary, we report the FAF, infrared imaging, and SD-OCT features of retinal astrocytic hamartomas in 4 patients with tuberous sclerosis. These imaging modalities allowed more sensitive detection of subtle tumors compared to conventional ophthalmoscopy and color fundus photography. Infrared imaging and SD-OCT were the most sensitive techniques, but FAF was a useful adjunctive test to obtain greater contrast between lesions and surrounding retina. The high-resolution SD-OCT scans revealed *in vivo* structural details, such as hyperreflective dots, that were not visible with earlier OCT imaging, and they offered further insights into previously described correlations with histopathology. The ability to

monitor structural changes over time in astrocytic hamartomas using SD-OCT may be beneficial for monitoring the success of systemic chemotherapy in the treatment of various tuberous sclerosis tumors.

Acknowledgments

Funding/Support: Burroughs-Wellcome Program in Biomedical Sciences (SHT); Charles E. Culpeper Scholarship (SHT); Foundation Fighting Blindness (SHT); Hirschl Trust (SHT); Crowley Research Fund (SHT); Schneeweiss Stem Cell Fund (SHT); Joel Hoffmann Scholarship (SHT); Jonas Family Fund (SHT); Hartford/American Geriatrics Society (SHT); Eye Surgery Fund (SHT, TRB); Bernard Becker-Association of University Professors in Ophthalmology (SHT); Research to Prevent Blindness (SHT); National Eye Institute grants R01EY018213 (SHT), DoD TS080017-W81XWH-09-1-0575 (SHT), and R01EY015520 (JPG); and the Doris Duke Clinical Research Fellowship Program (LX).

Other Acknowledgements: We are grateful to the members of the photography department at the Edward S. Harkness Eye Institute, Columbia University, New York, NY, for their assistance in obtaining images for this case series. We also greatly appreciate the sharing of ideas and equipment by Professor R. Theodore Smith, MD, PhD, at the Harkness Eye Institute. Editorial assistance was provided by Jennifer L. Dalberth, Harkness Eye Institute.

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Biographies

Luna (Lu Na) Xu, B.S., B.A., is a fourth-year medical student at Columbia University College of Physicians and Surgeons. She was a recipient of the 2010–2011 Doris Duke Clinical Research Fellowship to medical students, which funded her year of research at the Edward S. Harkness Eye Institute under the mentorship of Dr. R. Theodore Smith and Dr. Gaetano Barile. She plans on pursuing a career in ophthalmology and is continuing her work as a clinical researcher in Dr. Smith's lab.

Jonathan P. Greenberg received his medical degree in 2008 from the University of the Witwatersrand, South Africa. He is currently a post-doctoral research fellow at the Edward S. Harkness Eye Institute, Columbia University. After his fellowship, he intends to pursue a residency in Ophthalmology in the United States.

Figure 1.

Case 1. A 12-year-old boy with tuberous sclerosis complex presented with an astrocytic hamartoma in the left eye. **(Top left)** Fundus photos and **(middle left)** fundus autofluorescence (FAF) images of the right eye appeared normal. **(Bottom left)** Infrared image of the right eye showed a small area of hyporeflexivity superior to the inferotemporal arcades. **(Bottom left, insert)** Corresponding spectral domain optical coherence tomography (SD-OCT) imaging revealed thickening of the retinal nerve fiber layer in this region. **(Top right)** The fundus image of the left eye showed an elevated, opaque heterogeneous lesion with glistening spherules. **(Middle right)** FAF of this lesion showed multiple intensely hyperautofluorescence spots. **(Bottom right)** Corresponding SD-OCT scans revealed a dramatic transition from normal to abnormal retina, with no visible extension beyond the main body of the tumor. Within the lesion, SD-OCT revealed numerous hyperreflective dots and optically empty spaces, neither of which demonstrated posterior shadowing (**black arrow**).

Figure 2.

Case 2. A 13-year-old boy with tuberous sclerosis complex presented with bilateral astrocytic hamartomas. (**Top row**) Color fundus photos showed a tumor along the inferotemporal arcades of each eye. (**Top row, left**) Color fundus photo of the right eye demonstrated a second, subtle lesion at the inferotemporal extreme of the field (**green arrow**). (**Second row, left**) Fundus autofluorescence (FAF) of the right eye showed two hypoautofluorescent lesions. Hyperautofluorescent spots were present toward the center of the more superior lesion. The far inferior lesion was visualized more easily than on the color photo (**green arrow**). (**Second row, right**) FAF of the lesion in the left eye showed hypoautofluorescence with faintly hyperautofluorescent dots in its center. (**Third row**) Spectral-domain optical coherence tomography (SD-OCT) of the corresponding lesion in the second row showed moth-eaten optically empty spaces without posterior shadowing at all depths of the lesion (**white arrows**). Hyperreflective dots were also observed within the lesion (**black arrow**). (**Bottom row**) A three-dimensional view of the right eye co-localized the empty spaces on SD-OCT with the hyperautofluorescent spots on en face FAF. Similar co-localization was observed in the left eye (image not shown).

Figure 3.

Case 3. A 9-year-old girl with tuberous sclerosis complex presented with bilateral astrocytic hamartomas. **(Top left)** Fundus photos of the right eye showed a faint gray-colored lesion close to the optic nerve. **(Middle left)** Fundus autofluorescence (FAF) image of the lesion of the right eye demonstrated hypoautofluorescence. **(Bottom left)** Corresponding spectral domain optical coherence tomography (SD-OCT) revealed small white dots with posterior shadowing (**black arrows**). **(Top right)** Fundus photos of the left eye showed faint astrocytic hamartomas close to the optic nerve. The lesion along the inferotemporal arcade was visible but was even more subtle. **(Middle right)** FAF image of the left eye demonstrated 3 distinct hypoautofluorescent lesions, all visualized more easily than on color

photos. (**Bottom right**) SD-OCT of the lesion inferior to the disc showed moth-eaten empty spaces without posterior shadowing (**white arrows**).

Figure 4.

Case 4. An 11-year-old girl with tuberous sclerosis complex presented with an astrocytic hamartoma of the left eye. **(Top left)** Fundus image of the right eye initially appeared normal. After localization with fundus autofluorescence (FAF), infrared, and spectral domain optical coherence tomography (SD-OCT), the occult lesion became somewhat visible as a very faint discoloration and slight obscuration of the vessel. **(Second and fourth rows, left)** FAF and Infrared images of the right eye revealed an area of hypofluorescence and hyporeflexivity, respectively, close to the superotemporal arcades. **(Third row, left)** Corresponding SD-OCT of the lesion demonstrated thickening of the retinal nerve fiber layer (RNFL) with compression of the inner retina. **(Top right)**

Fundus photo of the left eye revealed a gray-colored lesion overlying the inferotemporal arcades. **(Second and fourth row, right)** FAF and infrared imaging of the lesion showed hypoautofluorescence and hyporefectivity, respectively. **(Third row, right)** Corresponding SD-OCT of the lesion demonstrated thickening of the RNFL. Shadowing caused by the lesion prevented adequate visualization of the retinal layers deep to the tumor. The vitreous was adherent to the inner surface of the lesion.