Published in final edited form as:

Retina. 2010 September ; 30(8): 1217–1222. doi:10.1097/IAE.0b013e3181cea5a5.

Fundus Autofluorescence and Optical Coherence Tomography of Congenital Grouped Albinotic Spots

David Y. Kim, MD^a, John C. Hwang, MD^a, Anthony T. Moore, FRCOphth^{b,c}, Alan C. Bird, MD^{b,c}, and Stephen H. Tsang, MD, PhD^{a,d,†}

^aBernard and Shirlee Brown Glaucoma Laboratory, Department of Ophthalmology, Columbia University College of Physicians and Surgeons, New York, New York

^bMedical Retina Service, Moorfields Eye Hospital, London, United Kingdom

^cInstitute of Ophthalmology, University College London, London, United Kingdom

^dDepartment of Pathology & Cell Biology, Columbia University College of Physicians and Surgeons, New York, New York

Abstract

Purpose—To describe fundus autofluorescence (FAF) and optical coherence tomography (OCT) in a series of patients with congenital grouped albinotic spots (CGAS).

Methods—Three eyes of three patients with CGAS were evaluated with FAF and OCT imaging to evaluate the nature of the albinotic spots.

Results—In all three eyes with CGAS, FAF imaging revealed autofluorescent spots corresponding to the albinotic spots seen on stereo biomicroscopy. One eye also had additional spots detected on FAF imaging that were not visible on stereo biomicroscopy or color fundus photographs. FAF imaging of the spots demonstrated decreased general autofluorescence as well as decreased peripheral autofluorescence surrounding central areas of retained or increased autofluorescence. OCT revealed a disruption in signal from the hyper-reflective layer corresponding to the photoreceptor inner and outer segment junction as well as increased signal backscattering from the choroid in the area of the spots. Fluorescein angiography (FA) demonstrated early and stable hyperfluorescence of the spots without leakage.

Conclusion—In this case series, FAF demonstrated decreased autofluorescence of the spots consistent with focal RPE atrophy or abnormal material blocking normal autofluorescence as well as areas of increased autofluorescence suggesting RPE dysfunction. OCT and FA findings suggest photoreceptor and RPE layer abnormalities. FAF and OCT are useful noninvasive diagnostic adjuncts that can aid in the diagnosis of GCAS, help determine extent of disease, and contribute to our understanding of its pathophysiology.

[†]Corresponding author: Stephen H. Tsang, MD, PhD, Department of Ophthalmology, Columbia University College of Physicians and Surgeons, 160 Fort Washington Avenue, Room 513, New York, NY 10032, Tel: (212) 342-1189, sht2@columbia.edu.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Financial Disclosure:

The authors have no commercial, proprietary, or financial interest in any of the products or companies described in this article.

Keywords

Congenital grouped albinotic spots; Grouped congenital pigmentation of the retina; Fundus autofluorescence; Optical coherence tomography; Polar bear tracks; Bear tracks; White dots

INTRODUCTION

Congenital grouped albinotic spots (CGAS), or “polar bear tracks,” is a disorder of the retinal pigment epithelium (RPE) characterized by multiple, variably-sized, sharply circumscribed, placoid, white lesions organized in patterns often resembling animal footprints. The lesions occur in one or both eyes and are generally more numerous and larger in the peripheral retina. It is speculated that the spots are focal changes of RPE cells in which a white material, possibly a precursor of melanin, is deposited instead of melanin granules.^{1–4}

The disorder is considered to be without functional consequence and patients typically have normal visual acuity, visual fields, color vision, dark adaptation, electroretinography, and electrooculography findings. However, Gass¹ reported a case of CGAS with severe visual loss caused by choroidal neovascularization, Parke et al⁵ reported a syndrome of microcephaly without mental retardation associated with spots quite similar to those in CGAS, and Battaglia and Iacono⁶ described a wide atrophic macular lesion and 20/400 vision in a patient with CGAS.

Fluorescein angiography (FA) and indocyanine green angiography (ICGA) characteristics of CGAS have been described. FA has shown variable degrees of transmission of choroidal fluorescence through the lesions without leakage or late staining^{4,7,8} ICGA has demonstrated both increasing hyperfluorescence as well as hypofluorescence of the lesions.^{6,8}

Fundus autofluorescence (FAF) as well as optical coherence tomography (OCT) have become powerful noninvasive diagnostic imaging modalities in evaluating the photoreceptor-RPE complex. To date, FAF and OCT findings have not been characterized for CGAS. The purpose of this case series is to report FAF and OCT findings in CGAS, which can assist the diagnosis and strengthen our understanding of the pathophysiology of CGAS.

METHODS

Patients diagnosed with CGAS were identified retrospectively from January 2004 to December 2008 at the Moorfields Eye Hospital, Medical Retina Service (London, UK) and the Edward S. Harkness Eye Institute of Columbia University Medical Center (New York, NY). Three patients were identified and medical records were reviewed. Data abstracted included patient demographics, ocular history, and best-corrected Snellen visual acuity. Color photographs, red-free photographs, fluorescein angiography, OCT, and FAF studies were reviewed.

FAF imaging was performed with a confocal scanning laser ophthalmoscope (cSLO, Heidelberg Retina Angiograph 2; Heidelberg Engineering, Dossenheim, Germany) after pupil dilation with topical tropicamide and phenylephrine. FAF imaging was performed using a 30° field of view at a resolution of 1536 × 1536 pixels. An optically pumped solid-state laser (488 nm) was used for excitation and a 495 nm barrier filter was used to modulate the blue argon excitation light. Standard procedure was followed for the acquisition of FAF images, including focus of the retinal image in the infrared reflection mode at 820 nm, sensitivity adjustment at 488 nm, and acquisition of 9 single 30° × 30° FAF images encompassing the entire macular area with at least a portion of the optic disc. The 9 single images were computationally averaged to produce a single frame with improved signal-to-noise ratio.

Optical coherence tomography (Stratus OCT, Carl Zeiss, Dublin, CA, USA) was performed on one patient. The acquisition protocol consisted of 512 A-scans over a 3-mm transverse scanning length for an optimal sampling rate of 400 A-scans per second. The fovea and regions containing the ophthalmoscopically visible spots were scanned. The precise location and orientation of each scan were determined using the simultaneous OCT grey-scale fundus images.

The study adhered to the tenets of the Declaration of Helsinki and received approval by the Institutional Review Board (Protocol #AAAD8731) of New York-Presbyterian Hospital (New York, NY). Medical charts were reviewed in compliance with the Health Insurance Portability and Accountability Act.

RESULTS

In this study, 6 eyes of one man and two women with CGAS were evaluated. The mean age was 37.2 years (range, 32–40 years). Unilateral involvement was found in all three patients. Mean best-corrected visual acuity was 20/15 in all eyes. Clinical examination showed typical manifestation of CGAS including multiple, variably-sized, sharply circumscribed, placoid, white lesions organized into groups. Some of the spots appeared to also contain dark gray pigment. In all affected eyes, the spots were found within the posterior pole.

In all three eyes with clinical findings of CGAS, FAF imaging revealed numerous well-defined lesions corresponding in location to the albinotic spots seen on stereo biomicroscopy. In one eye, FAF imaging also revealed autofluorescent spots not visible with indirect ophthalmoscopy or fundus photography (Figure 1. A and B).

FAF demonstrated variable autofluorescence of the spots (Figure 2. A through F). The majority of the spots demonstrated decreased autofluorescence. Some of the spots demonstrated reduced autofluorescence peripherally within the lesions with central areas of normal appearing or increased autofluorescence. These spots tended to be smaller and fewer in comparison to the other spots in the same eyes.

Fluorescein angiography performed in one patient demonstrated early and stable hyperfluorescence of the spots without leakage of dye (Figure 3).

Optical coherence tomography performed in one patient demonstrated a disruption in signal from the hyper-reflective layer of the retina corresponding to the photoreceptor inner and outer segment (IS/OS) junction in the area of the spots (Figure 4. A through C). In addition, there was increased signal backscattering from the choroid in the area of the spots.

DISCUSSION

CGAS is a rare disorder of the RPE characterized by white spots grouped into patterns resembling animal footprints. Diagnosis of CGAS is made by the typical appearance on fundus examination.^{1,7} However, one patient in our series had a group of spots seen on FAF imaging that was not visible on fundus biomicroscopy. In this case, FAF demonstrated more widespread involvement of the RPE than originally suspected on clinical exam alone.

FAF is a noninvasive imaging modality that relies on the stimulated emission of light from molecules, chiefly lipofuscin, in the RPE and can provide indirect information on the level of metabolic activity of the RPE.⁹ In essence, abnormal FAF signals derive from a change in the number or composition of fluorophores in the RPE cell cytoplasm (i.e., lipofuscin) or from the presence of absorbing or autofluorescent material anterior to the RPE. In addition, abnormal

tissue with fluorophores with spectral characteristics similar to RPE-lipofuscin may cause a corresponding increased FAF signal.¹⁰

In all our patients with CGAS, FAF of the spots demonstrated decreased autofluorescence. In retinal dystrophies, decreased FAF is thought to correspond to areas of reduced metabolism resulting from photoreceptor and/or RPE atrophy.^{11–13} The decrease in FAF seen in our patients may suggest atrophy in the area of the spots. Alternatively, the decreased FAF signal may be from blockage or absorption of normal autofluorescence caused by abnormal material, possibly a precursor of melanin as hypothesized by Gass,⁷ filling the RPE. Consistent with both hypotheses, fluorescein angiography has demonstrated early and stable hyperfluorescence without leakage consistent with an RPE window defect allowing transmission of choroidal fluorescence or staining of abnormal material.^{4,7,8} Karacorlu et al⁸ attributed uniform ICGA hyperfluorescence of the spots to staining of abnormal RPE material.

A few of the spots demonstrated reduced autofluorescence peripherally within the lesions with central areas of normal appearing or increased autofluorescence. Increased FAF signal is thought to correspond to accumulation of lipofuscin in the RPE or subretinal space. Excessive lipofuscin accumulation represents a common pathogenetic pathway in various degenerative and monogenetic retinal diseases and is believed to precede photoreceptor degeneration.^{14–17} The increased areas of FAF signal seen in our patients may suggest RPE dysfunction in the area of the spots. Alternatively, if the areas of decreased FAF signal are due to blockage or absorption from abnormal RPE material, the central areas of relatively increased autofluorescence within the lesions could be explained by less blockage or absorption of FAF signal. In Gass' observation, the abnormal white material comprising the spots appeared either diffusely distributed or concentrated more peripherally within the lesions consistent with the patterns of FAF signals seen in our patients.

Battaglia and Iacono⁶ believed variable ICGA behavior of the spots in their patient suggested different stages of disease. They hypothesized that hyperfluorescent spots represented gradual staining of abnormal material related to an earlier stage of disease and hypofluorescent spots indicated more advanced disease reflecting degeneration of the RPE and underlying choroid. The abnormal autofluorescence patterns seen in our patients could be consistent with the hypothesis that defective lipofuscin metabolism contributes to varying stages of disease in CGAS. The areas of increased FAF could suggest RPE dysfunction and the areas with decreased FAF may represent more advanced RPE atrophy. However, to date, the natural course of the lesions in CGAS remains unknown.

OCT of the hypoautofluorescent CGAS lesions demonstrated disrupted signals from the hyper-reflective layer of the retina corresponding to the IS/OS junction in the region corresponding to the spots. Early disorganization of the IS/OS boundary is a morphologic marker for photoreceptor damage in human^{18,19} and animal models.^{20,21} The increase in signal backscattering from the choroid, as seen in our patient, suggests loss of the normal RPE barrier since very little of the OCT signal travels through the RPE in normal eyes.²² All patients in our series were without visual complaints. However, microperimetry and multifocal electroretinography data may have revealed corresponding defects.

The lack of melanin pigment within the spots may result in the loss of antioxidative function within the RPE. One study looked at the rate of lipofuscin formation in pigmented versus albino rabbit RPE cells as well as pigment-rich versus pigment-poor bovine RPE cells.²³ These cells were subjected to oxidative stress and daily supplementation with photoreceptor outer segments. The melanin lacking cells accumulated significantly higher amounts of lipofuscin attributed to decreased intrinsic reducing capacity of melanin. It is feasible that the lack of melanin in the albinotic spots of CGAS could result in loss of antioxidative function in RPE

cells with eventual dysfunction and atrophy of the RPE-photoreceptor complex. Shields and Ts'o²⁴ reported histologic findings in grouped congenital pigmentation of the retina, also known as “bear tracks,” which showed normal photoreceptors overlying focal areas of increased concentration of pigment granules in otherwise normal RPE cells. There are no reported histologic studies of CGAS to date. However, the lack of melanin within the lesions and subsequent diminished antioxidative capacity may result in a less benign pathological response in CGAS.

FAF and OCT are useful noninvasive diagnostic adjuncts to identify and determine disease extent in CGAS. FAF is a more sensitive marker than clinical exam alone and is less invasive than FA or ICGA. FAF and OCT findings suggest abnormalities at the level of the RPE and overlying photoreceptors. Despite these observations, the pathophysiology of CGAS remains unclear and the natural history of CGAS is unknown with few reported cases. More studies are required to determine the precise etiology of CGAS.

Acknowledgments

Funding/Support:

This study is supported by a fellowship from the Burroughs-Wellcome Program in Biomedical Sciences, the Dennis Jahnigen Award from the American Geriatrics Society, the Hirschl Charitable Trust, the Joel Hoffmann Foundation, the Schneeweiss Stem Cell Fund, Crowley Research Fund, the Association of University Professors in Ophthalmology–Research to Prevent Blindness and Eye Surgery Fund, the Foundation Fighting Blindness, and grant EY004081 from the National Institutes of Health.

REFERENCES

1. Gass JDM. Focal congenital anomalies of the retinal pigment epithelium. *Eye* 1989;3:1–18. [PubMed: 2591592]
2. Fuhrmann C, Bopp S, Laqua H. Congenital grouped albinotic spots: a rare anomaly of the retinal pigment epithelium. *Ger J Ophthalmol* 1992;1(2):103–104. [PubMed: 1477623]
3. Kadoi C, Hayasaka S, Hayasaka Y, et al. Bilateral congenital grouped pigmentation of the retina in one girl and bilateral congenital albinotic spots of the retina in her sister. *Retina* 1999;19(6):571–572. [PubMed: 10606465]
4. Nakamura N, Hayasaka S, Nagaki Y, et al. Bilateral congenital grouped retinal pigment epithelial albinotic nevi. *Ann Ophthalmol* 2000;32(4):333–335.
5. Parke JT, Riccardi VM, Lewis RA, Ferrell RE. A syndrome of microcephaly and retinal pigmentary abnormalities without mental retardation in a family with coincidental autosomal dominant hyperreflexia. *Am J Med Genet* 1984;17(3):585–594. [PubMed: 6711609]
6. Battaglia Parodi M, Iacono P. Indocyanine green angiography pattern of congenital grouped albinotic retinal pigment epithelial spots. *Semin Ophthalmol* 2004;19(3–4):114–116. [PubMed: 15590550]
7. Gass, JDM. Stereoscopic atlas of macular diseases: diagnosis and treatment. ed. 4. St. Louis: CV Mosby; 1997. p. 816–819.
8. Karacorlu SA, Karacorlu M, Ozdemir H, Sanisoglu H. Indocyanine green angiographic findings in congenital grouped albinotic spots. *Retina* 2006;26(4):470–472. [PubMed: 16603969]
9. Delori FC, Dorey CK, Staurenghi G, et al. In vivo fluorescence of the ocular fundus exhibits retinal pigment epithelium lipofuscin characteristics. *Invest Ophthalmol Vis Sci* 1995;36:718–729. [PubMed: 7890502]
10. Holz, FG.; Schmitz-Valckenberg, S.; Bird, AC.; Spaide, RF. Atlas of Fundus Autofluorescence Imaging. Berlin: Springer-Verlag; 2007. p. 71–73.
11. Robson AG, Michaelides M, Saihan Z, et al. Functional characteristics of patients with retinal dystrophy that manifest abnormal parafoveal annuli of high density fundus autofluorescence; a review and update. *Doc Ophthalmol* 2008;116(2):79–89. [PubMed: 17985165]
12. Tsui I, Chou CL, Palmer N, et al. Phenotype-genotype correlations in autosomal dominant retinitis pigmentosa caused by RHO, D190N. *Curr Eye Res* 2008;33(11):1014–1022. [PubMed: 19085385]

13. Tsui I, Fuchs BS, Chou CL, et al. Non-vascular vision loss in pseudoxanthoma elasticum. *Doc Ophthalmol* 2008;117(1):65–67. [PubMed: 18034271]
14. Sparrow JR, Nakanishi K, Parish CA. The lipofuscin fluorophore A2E mediates blue light-induced damage to retinal pigmented epithelial cells. *Invest Ophthalmol Vis Sci* 2000;41:1981–1989. [PubMed: 10845625]
15. Dorey CK, Wu G, Ebenstein D. Cell loss in the aging retina: relationship to lipofuscin accumulation and macular degeneration. *Invest Ophthalmol Vis Sci* 1989;30:1691–1699. [PubMed: 2759786]
16. Lima LH, Cella W, Greenstein VC, et al. Structural assessment of hyperautofluorescent ring in patients with retinitis pigmentosa. *Retina* 2009;29(7):1025–1031. [PubMed: 19584660]
17. Wang NK, Chou CL, Lima LH, et al. Fundus autofluorescence in cone dystrophy. *Doc Ophthalmol* 2009 Oct;119(2):141–144. [PubMed: 19340470]
18. Ergun E, Hermann B, Wirtitsch M, et al. Assessment of central vision function in Stargardt's disease/fundus flavimaculatus with ultra-high resolution optical coherence tomography. *Invest Ophthalmol Vis Sci* 2005;46:310–316. [PubMed: 15623790]
19. Witkin AJ, Ko TH, Fujimoto JG, et al. Ultra-high resolution optical coherence tomography assessment of photoreceptors in retinitis pigmentosa and related diseases. *Am J Ophthalmol* 2006;142:945–952. [PubMed: 17157580]
20. Horio N, Kachie S, Hori K, et al. Progressive change of optical coherence tomography scans in retinal degeneration slow mice. *Arch Ophthalmol* 2001;119:1329–1332. [PubMed: 11545639]
21. Huang Y, Cideciyan AV, Papastergiou GI, et al. Relation of optical coherence tomography to microanatomy in normal and rd chickens. *Invest Ophthalmol Vis Sci* 1998;39:2405–2416. [PubMed: 9804149]
22. Scheufler TA, Witkin AJ, Schocket LS, et al. Photoreceptor atrophy in acute posterior multifocal placoid pigment epitheliopathy demonstrated by optical coherence tomography. *Retina* 2005;25(8):1109–1112. [PubMed: 16340549]
23. Sundelin SP, Nilsson SE, Brunk UT. Lipofuscin-formation in cultured retinal pigment epithelial cells is related to their melanin content. *Free Radic Biol Med* 2001;30(1):74–81. [PubMed: 11134897]
24. Shields JA, Ts'o MO. Congenital grouped pigmentation of the retina. Histopathologic description and report of a case. *Arch Ophthalmol* 1975;93(11):1153. [PubMed: 1191104]

Figure 1.

Color fundus photograph (A) and corresponding FAF image (B) in the superotemporal field of one eye in which FAF imaging revealed spots not visible with biomicroscopy. This patient also had spots with corresponding FAF lesions in the macula (see Figure 2A and 2B). FAF = fundus autofluorescence.

Figure 2. Color fundus photographs (**A, C, and E**) and corresponding FAF images (**B, D, and F**) of spots in three patients demonstrating decreased general autofluorescence as well as decreased peripheral autofluorescence surrounding central areas of higher FAF signal. FAF = fundus autofluorescence.

Figure 3. Fluorescein angiography of the spots demonstrated, in progressive time frames (**A**, **B**, **C**, and **D**), early and stable hyperfluorescence of the spots without leakage of dye.

Figure 4. OCT (A) with corresponding OCT-generated fundus image (B) and FAF image (C) demonstrating disruption in signal from the hyper-reflective layer of the retina associated with the photoreceptor inner and outer segment junction. In addition, choroidal backscattering is increased in the area of the spots indicating abnormal RPE. Solid bars on the OCT scan mark the location of the spots, dashed line on the FAF image marks the location of the scan line. OCT = optical coherence tomography, FAF = fundus autofluorescence.