Fundus albipunctatus photoreceptor microstructure revealed using adaptive optics scanning light ophthalmoscopy

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ABSTRACT

Purpose: Fundus albipunctatus is an inherited cause of congenital stationary night blindness. The objective of this report is to describe structural changes occurring in a macular phenotype of a novel RDH5 mutation producing fundus albipunctatus using high-resolution in vivo imaging. A 62-year-old male with longstanding night blindness underwent imaging and genetic evaluation. High-resolution images of the photoreceptor mosaic were compared to those of a healthy subject. Results of a comprehensive ophthalmic evaluation and genetic testing with imaging underwent imaging and genetic evaluation. High-resolution images of the photoreceptor mosaic were compared to those of a healthy subject. Results of a comprehensive ophthalmic evaluation and genetic testing with imaging demonstrating a retinal dehydrogenase mutation c.388C>T, p.Gln130* and c.665T>C, p.Leu222Pro). OCT demonstrated perifoveal photoreceptor and outer retinal abnormalities, which corresponded to a window defect with late staining on FA. OCT-A demonstrated normal retinal vasculature with patchy areas of non-perfusion in the choriocapillaris. Macular abnormalities in both eyes were imaged using AOSLO to assess cone and rod photoreceptor architecture. While clinical features are consistent with a primary rod disorder, confocal AOSLO showed a paucity of normal cones with a small spared central island in both eyes. Rods appeared larger and more irregular throughout the macula. Non-confocal split detection AOSLO imaging revealed the presence of cone inner segments in dark regions of confocal imaging, indicating some degree of photoreceptor preservation.

Conclusions and Importance: The AOSLO imaging of this particular macular phenotype of fundus albipunctatus demonstrates some of the structural photoreceptor abnormalities that occur in this condition, adding insight to the possibility that gene therapy could play a future role in treating this condition.

1. Introduction

Fundus albipunctatus is an autosomal recessive form of congenital stationary night blindness associated with 11-cis retinol dehydrogenase (RDH5) gene mutations. While phenotypic variability exists, the condition typically presents with numerous discrete white-yellow flecks in the retinal periphery, which vary in shape and density among patients and according to age.1,2 Classic descriptions include normal visual acuity, visual fields, and color vision, with a stationary component of impaired scotopic vision that improves following prolonged dark adaptation.3 More recent reports describe variable macular dysfunction and cone dystrophy in older patients.4 Physiologic studies have
characterized these photopic abnormalities, while very few investigations have examined the structural details of photoreceptors in patients with significant maculopathy. This report describes the findings of in-vivo high-resolution imaging of the photoreceptor changes in fundus albipunctatus with macular dystrophy, which include a degree of structural preservation revealed by AOSLO.

1.1. Case report

A 62-year-old male presented with longstanding poor night vision, beginning around 8 years of age, and stable visual acuity with little symptomatic progression over many years. On the basis of the clinical appearance, the patient carried a diagnosis of Stargardt’s disease without confirmatory genetic testing. He had no other past ocular or surgical history, denied any family history or use of any medications associated with ocular toxicity. His only past medical history included mild peripheral arterial disease. Review of systems was unremarkable for any systemic complaints.

Visual acuity was 20/25 in each eye. Pupillary examination and intraocular pressures were within normal limits. Ishihara color testing was reduced to six of 12 correct plates in each eye. The anterior segment was notable for mild nuclear sclerotic cataracts in both eyes. Fundoscopic examination revealed a clear vitreous with normal optic nerves and vasculature. In both eyes, there was a flat and well circumscribed area of perifoveal atrophy with retinal pigment epithelial (RPE) mottling (Fig. 1A). Discrete white-yellow flecks without areas of confluence were present peripheral to the vascular arcades, most dense in the mid peripheral retina which appeared to coincide with retinal flecks. A granular staining was seen in later frames, corresponding to the atrophic bull’s eye pattern visible on fundoscopy (Fig. 1D). A granular staining was seen in the peripheral retina which appeared to coincide with retinal flecks. A 24–2 white stimulus III Humphrey visual field demonstrated bilateral central scotomas with intact foveal fixation. OCT-A confirmed normal retinal vasculature (Fig. 2A–C), with the exception of patchy areas of non-perfusion at the level of the choriocapillaris (Fig. 2D). Genetic testing (Spark Therapeutics, Inherited Retinal Disease Panel, Philadelphia, PA, USA), revealed a novel compound heterozygous RDH5 mutation (c.388C>T, p.Gln130*; c.665T>C, p.Leu222Pro), consistent with a diagnosis of autosomal recessive fundus albipunctatus.

Reflectance confocal AOSLO imaging of the photoreceptor mosaic showed central foveal preservation, with marked disruption in the surrounding area (Fig. 3A). Within the preserved foveal area, the cones appear larger and less densely packed when compared to a normal subject (Fig. 3B). The cones immediately outside of this area were also more sparse and darker in appearance. Non-confocal split-detection images were taken simultaneously and are co-registered with the confocal images (Fig. 3C and D). Split-detection images are believed to highlight translucent structures such as the inner segments of photoreceptors, and in this case the patient’s image (Fig. 3C) indicates large intact inner segments in the areas immediately outside the spared foveal cones, and are of much larger and appear with higher contrast than the corresponding structures in a normal fovea (Fig. 3D). The en face perspective can also be shown with the OCT data (Fig. 4), where a 3 μm-thick slab placed 40 μm above the Bruch’s membrane can clearly show the areas where photoreceptors are disrupted around the fovea. The region of spared foveal cones can be seen clearly in the center (Fig. 4B). In another confocal image at approximately two-thirds of the distance between the fovea and optic nerve (Fig. 5A), cones continue to appear larger than normal with an irregular distribution. The intervening rod cells, which are normally not well imaged in this area owing to their small size, were distinctly brighter than the surrounding disrupted cones and larger in diameter (Fig. 5A) when compared to those of normal eyes (Fig. 5B). Non-confocal split detection AOSLO images (Fig. 5C) revealed intact inner segments of some of the dark cone cells in the corresponding confocal images suggestive of partial preservation of photoreceptor architecture.

Details of the findings and the current absence of therapeutic options were discussed with the patient. He declined an offer of genetic counseling referral.
2. Discussion

Fundus albipunctatus was initially described as a form of congenital stationary night blindness characterized by minimal progression over time. However, cone dystrophy in a subset of patients has been reported, especially in older individuals. It has been hypothesized that the progressive cone dysfunction seen in fundus albipunctatus may be related to impaired RPE function due to the RDH5 gene mutation, or from the direct effects of a depleted 11-cis-retinal supply to the cone cells. Structural abnormalities have been described in the outer retina and photoreceptor inner segment-outer segment junction. Ocular aberrations limit the ability to resolve the photoreceptors using conventional ophthalmic imaging devices. AOSLO provides greater detail in characterizing microstructural abnormalities of various retinal diseases.

Previous studies of fundus albipunctatus patients with RDH5 mutations imaged with AOSLO have reported cone irregularities and mosaic disruptions even in patients with minimal or no visible macular pathology on fundoscopy or OCT, with the conclusion that cones are both fewer in number and irregularly spaced. These cone cell abnormalities may also represent early findings prior to progression to a macular phenotype, in contrast to the more advanced form seen in our patient in which the macular dystrophy was readily apparent on both clinical exam and multimodal imaging. While some variability has been described in the cone mosaic architecture and cell density even in normal subjects, it is reasonable to conclude that the changes observed in the AOSLO confocal image of the cone mosaic of our patient are largely due to macular pathology.

Additionally, non-confocal split detection AOSLO imaging provides visualization of the mosaic of intact photoreceptor inner segments. The split-detection images in our study suggest a partial preservation of photoreceptor inner segments despite their elongated and disrupted appearance on OCT, similar to previous reports. In different retinal dystrophies, AOSLO reports have also described a similar structural preservation despite abnormal function. This interpretation attributes the dark appearance of certain photoreceptors to a waveguiding dysfunction of metabolic origin without complete loss of the cell body.

Notably, while the patient’s original diagnosis of Stargardt’s disease was upended by genetic testing, the AOSLO findings are helpful for explaining the patient’s clinical presentation. Previous studies using AOSLO in Stargardt’s disease have revealed increased cone and rod spacing, with reduced foveal cone density and enlarged cone size, and dark cones thought to be associated with foreshortened outer segments. These findings are similar to our patient’s photoreceptor characteristics on AOSLO, except for the profound sparing observed in the central fovea. Indeed, AOSLO appears to be better able to characterize the photoreceptor status than traditional imaging modalities.

Some limitations of our report include that it is based upon a single clinical subject and that we were unable to perform high-resolution AO imaging of the peripheral retinal flecks, which were located beyond the accessible field of the current AOSLO instrument. Electroretinographic studies may have provided further additional functional data but would offer little to the characterization of cone photoreceptor microstructure.

In summary, AOSLO imaging of this macular phenotype of fundus albipunctatus has demonstrated some of the structural photoreceptor abnormalities, which characterize RDH5 retinopathy. The finding of...
partial preservation of the photoreceptor inner segments despite an advanced macular dystrophy, indicates a persistence of structural integrity that could be amenable to future therapies.

**Patient consent**

Verbal consent of the patient and the healthy control were obtained for publication. This report does not contain any personal information that could lead to the identification of either the patient or the control.

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Conflicts of interest

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Authorship

All authors attest that they meet the current ICMJE criteria for authorship.

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Fig. 5. AOSLO scans taken at retinal eccentricities of 10° nasal from the fovea in the right eye of both the patient (A,C) and the healthy control (B,D). The confocal scans are shown above (A,B) and the non-confocal split detection images are shown below (C, D). The patient has a degree of cone photoreceptor inner segment preservation in this nasal region which is just outside the macular lesion seen on fundus photography in Fig. 1. There is, however, a lower spatial density of these cells overall when compared to a similar location in the healthy control subject’s eye. Rod photoreceptors, which are smaller than cones, populate most of the area imaged. The rod size appears larger in (A) and their inner segments are more visible in (C) compared to a matched area in the healthy control subject’s eye (D). In the normal control, the rod photoreceptor inner segments are not discernible from the large cones. Of note, the large dark lines in (A), (B), and (D) indicate shadow artifacts from large blood vessels and are normal features in AOSLO images. All scans are 250 μm by 250 μm, and the scale bar in (A) indicates a length of 50 μm.