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Case Report

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Supernormal foveal photoreceptor density in Alport syndrome: A case report

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Abstract

Purpose: To investigate foveal photoreceptor configuration in Alport syndrome, a rare inherited disease characterized by Collagen IV dysfunction.

Methods: Adaptive optics scanning laser ophthalmoscope (AOSLO) *in vivo* imaging of the foveal center and quantitative analysis of cone photoreceptor topography in a 17-year-old male patient with Alport syndrome presenting absence of a foveal avascular zone (FAZ) and foveal hypoplasia in both eyes.

Results: Cone density analysis based on AOSLO images revealed an unusual linear cone topography profile displaying supernormal densities within the fovea (z-scores up to + 3.57 and + 2.97 in right and left eyes, respectively).

Conclusion: Foveal hypoplasia has previously been associated with normal or reduced cone density. Our observation is the first case of disease-related supernormal cone density within the foveola, shedding light upon the role of Collagen IV in foveal maturation.

Keywords
Alport syndrome, retina, foveal hypoplasia, adaptive optics, cone density, supernormal, increased

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Introduction

Alport syndrome is an inherited multisystem disease caused by mutations in genes encoding collagen type IV, a major component of basement membranes.[1,2] The prevalence is estimated to be between 1:5000 and 1: 53,000.[3] Autosomal recessive Alport syndrome is caused by mutations in *COL4A3* or *COL4A4* located on chromosome 2, accounting for 15% of the cases.[2] X-linked Alport syndrome due mutations in *COL4A5* comprises the remaining 85% of cases.[1] While the leading pathology is progressive nephropathy, various ocular manifestations have been reported. Most commonly anterior lenticonus and dot and fleck retinopathy are diagnosed.[4] Recently, abnormalities of the foveal avascular zone and foveal hypoplasia were identified.[5] We here report the first adaptive optics scanning laser ophthalmoscope (AOSLO) image analysis of cone photoreceptor topography in an Alport syndrome patient with foveal hypoplasia, revealing an unusual foveal organization with increased cone density.

Case presentation

A 17-year-old male presented in the Department of Ophthalmology at the University Hospital Bonn with clinically and genetically confirmed Alport syndrome (homozygote mutation in *COL4A4*). The patient provided informed written consent to participate in the study. The study has been approved by the ethics committee at the medical faculty of the Rheinische Friedrich-Wilhelms-Universität Bonn. The study was conducted according to the tenets of the Declaration of Helsinki. Best corrected visual acuity (BCVA) was 1.0 and 0.8 (right and left eye

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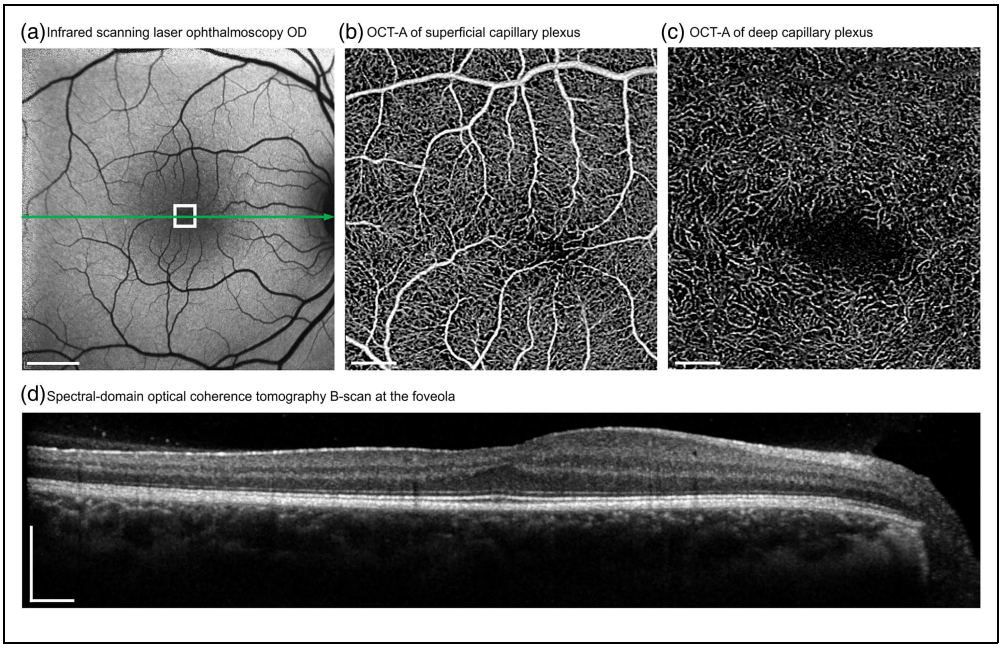

Figure 1. Retinal features in a case of Alport syndrome on multimodal imaging. (a) Infrared scanning laser ophthalmoscope image of the right eye and image location of adaptive optics scanning laser ophthalmoscopy montage (see Figure 2) marked by white rectangle. The green line indicates the location of the b-scan shown in d (b) Optical coherence tomography angiography (OCT-A), demonstrating complete absence of a foveal avascular zone (FAZ) in the superficial capillary plexus. (c) An oval shaped FAZ is present in the deep capillary plexus. (d) Spectral-domain optical coherence tomography (SD-OCT) central b-scan encompassing the fovea, presenting a grade 2 foveal hypoplasia. Scale bars in (a): 5°, (b) and (c): 2°, (d): 400 µm.

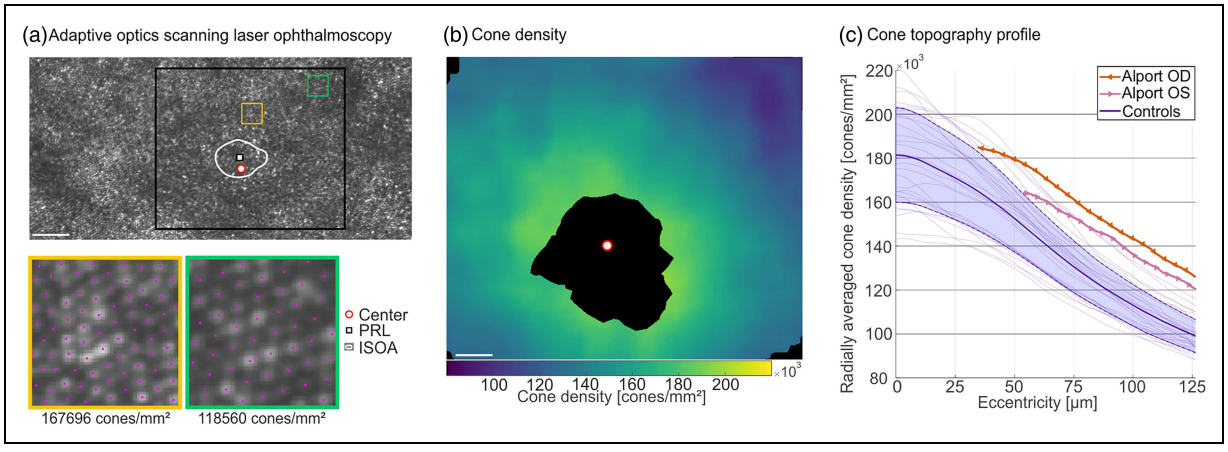

Figure 2. Abnormal foveal topography in Alport syndrome. (a) Adaptive optics scanning laser ophthalmoscopy (AOSLO) image montage around the preferred retinal locus of fixation (PRL, black-white square). The white outline is the isocontour area (ISOA) of fixation. The center of cone topography is marked by the red-white circle. Central vasculature appears as darker shadows. Yellow frame indicates zoomed-in area at ≈ 15 arcmin (67.5 µm), green frame at ≈ 30 arcmin (135.4 µm) distance to the center and purple dots annotated locations of single cones. The black outline marks the location used for cone density analysis. (b) Two-dimensional map of cone density of the right eye, unresolved area blacked-out. (c) Radially averaged cone density compared to normal controls (individual profiles with bold line = median ± 1 standard deviation, N = 28). Scale bars in (a): 10 arcmin; (b): 5 arcmin.

respectively). Multimodal imaging revealed foveal hypoplasia (Thomas classification grade 2, Figure 1a and d) and absence of a foveal avascular zone (FAZ) in the superficial capillary plexus (SCP, Figure 1b).[5] Confocal AOSLO *en-face* imaging with 0.85 degree imaging field size was performed in both eyes, and image montages were created covering about 1.8 degree of visual angle centered around the preferred retinal locus of fixation (PRL) (Figure 2a). Cone photoreceptor structure appeared normal, and outer segment centers were marked with

Matlab based semi-manual annotation tools.[6] Photoreceptor topography was analyzed within the central 70 arcmin diameter around the PRL, subsequently cropped to an area matching normative data (Figure 2a).[6] In both eyes, a small central area was excluded from the analysis due to unresolved photoreceptors (Figure 2b). Maximum cone density within the resolved area was 195,930 cones/mm^2 in the right eye (Figure 2b) and 186,210 cones/mm^2 in the left eye. In the following analysis, cone densities were defined as supernormal if the z-score was greater than + 2 z-scores compared to previously reported normal controls (N = 28) at the respective eccentricity (Figure 2c).[6] Radially averaged cone density was 184,867 cones/mm^2 (+ 1.14 z-scores) at 35 µm, 176,940 cones/mm^2 (+ 2.03) at 55 µm and 123,122 cones/mm^2 (+ 3.57) at 130 µm from the center of cone topography for the right eye. Cone densities in the left eye were increased as well, with + 1.13 z-scores at 55 µm and + 2.97 z-scores at 130 µm eccentricity (Figure 2c).[6] Notably, the radially averaged cone density profile showed a linear decrease with eccentricity (OD: −692 (cones/mm^2)/µm, OS: −631 (cones/mm^2)/µm), unlike healthy controls which present a more sigmoidal decrease function. Fixation stability, assessed by AOSLO-microstimulation, was within normal or slightly higher than normal range (isocontour area (ISOA) of fixation OD: 99 arcmin^2, ISOA OS: 138 arcmin^2). The PRL was offset from the cone topography center superiorly (OD: 3 arcmin and OS: 3.5 arcmin), a pattern that is also observed in healthy eyes.[6]

Discussion

Altered cone density profiles in ocular diseases presenting with foveal hypoplasia have previously been associated with normal or reduced cone density. In aniridia, eyes showed reduced cone density within the central 5°, with a flat peak at the foveal center.[7] In Patients with albinism, normal or reduced cone densities were identified, which correlated with the grade of hypoplasia and outer segment length.[8] Unlike these reports, our patient with Alport syndrome had an abnormal linear cone profile, resulting in a ring of higher-than-normal cone densities within the foveola. In general, mechanical leeway of the retinal layers is crucial for foveal specialization. While extrusion of inner retinal layers facilitates foveal pit formation, cone elongation and centripetal migration are a hallmark of the maturation of the outer retina.[9] In such light, we hypothesize that the mechanical foveal architecture in Alport syndrome is considerably different than normal. Collagen IV is a major component of basement membranes, a structural protein shown to play an important role both in angiogenesis and neuronal guidance during development.[10] The absence or misfolding of a major chain of collagen IV likely leads to incomplete foveal pit formation because vascular growth is unhindered and pit development seems to occur only in absence of blood vessels.[9] Changes in internal limiting membrane structure might further affect anchoring of Müller cells that are usually forming a functional unit with photoreceptors. Together, these distinct retinal environmental and mechanical circumstances appear to facilitate increased centripetal cone migration in Alport syndrome. Generally, cone density is an increasingly relevant readout parameter promising to be a sensitive endpoint in future clinical trials for treatment of retinal disease. Here, we demonstrate that a so far unknown disease related mechanism can reshape the foveal cone profile. To our best knowledge, it is the first report of overall supernormal cone densities in the foveola of any retina.

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Authorship

All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Compliance with ethics guidelines

The study has been approved by the ethics committee at the medical faculty of the Rheinische Friedrich-Wilhelms-Universität Bonn. The study was conducted according to the tenets of the Declaration of Helsinki. The patient provided informed consent to participate in the study.

Data availability

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request

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Declaration of conflicting interests

The author(s) declared the following potential conflicts of interest GQ3 with respect to the research, authorship, and/or publication of this article: The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Kristina Hess has received technical support from Heidelberg Engineering and Carl Zeiss Medic Tec AG. She has received financial support for presentations from Novartis GmbH. Frank G. Holz has received financial support as consultant from Heidelberg Engineering and Zeiss. He has received study grants from Heidelberg Engineering, Zeiss and Centervue. Julius Ameln, Jenny L. Reiniger and Wolf M. Harmening declare that they have no conflict of interest.

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