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Short Communication

Dysflective cones: Visual function and cone reflectivity in long-term follow-up of acute bilateral foveolitis

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ABSTRACT

Purpose: Confocal adaptive optics scanning laser ophthalmoscope (AOSLO) images provide a sensitive measure of cone structure. However, the relationship between structural findings of diminished cone reflectivity and visual function is unclear. We used fundus-referenced testing to evaluate visual function in regions of apparent cone loss identified using confocal AOSLO images.

Methods: A patient diagnosed with acute bilateral foveolitis had spectral-domain optical coherence tomography (SD-OCT) (Spectralis HRA + OCT system [Heidelberg Engineering, Vista, CA, USA]) images indicating focal loss of the inner segment-outer segment junction band with an intact, but hyperreflective, external limiting membrane. Five years after symptom onset, visual acuity had improved from 20/80 to 20/25, but the retinal appearance remained unchanged compared to 3 months after symptoms began. We performed structural assessments using SD-OCT, directional OCT (non-standard use of a prototype on loan from Carl Zeiss Meditec) and AOSLO (custom-built system). We also administered fundus-referenced functional tests in the region of apparent cone loss, including analysis of preferred retinal locus (PRL), AOSLO acuity, and microperimetry with tracking SLO (TSLO) (prototype system). To determine AOSLO-corrected visual acuity, the scanning laser was modulated with a tumbling E consistent with 20/30 visual acuity. Visual sensitivity was assessed in and around the lesion using TSLO microperimetry. Complete eye examination, including standard measures of best-corrected visual acuity, visual field tests, color fundus photos, and fundus auto-fluorescence were also performed.

Results: Despite a lack of visible cone profiles in the foveal lesion, fundus-referenced vision testing demonstrated visual function within the lesion consistent with cone function. The PRL was within the lesion of apparent cone loss at the fovea. AOSLO visual acuity tests were abnormal, but measurable: for trials in which the stimulus remained completely within the lesion, the subject got 48% correct, compared to 78% correct when the stimulus was outside the lesion. TSLO microperimetry revealed reduced, but detectible, sensitivity thresholds within the lesion.

Conclusions and Importance: Fundus-referenced visual testing proved useful to identify functional cones despite apparent photoreceptor loss identified using AOSLO and SD-OCT. While AOSLO and SD-OCT appear to be sensitive for the detection of abnormal or absent photoreceptors, changes in photoreceptors that are identified with these imaging tools do not correlate completely with visual function in every patient. Fundus-referenced vision testing is a useful tool to indicate the presence of cones that may be

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amenable to recovery or response to experimental therapies despite not being visible on confocal AOSLO or SD-OCT images.

1. Introduction

Advances in ophthalmic imaging technology, such as spectral-domain optical coherence tomography (SD-OCT) and confocal adaptive optics scanning laser ophthalmoscopy (AOSLO), allow for detailed and sensitive measures of structural changes in the retina, including photoreceptors.[1,2] However, the relationship between images of cone structure and visual function is not always clear. This ambiguous relationship has been reported in acute macular neuroretinopathy (AMN), a disease characterized by selective injury to the cone photoreceptors with retention of the normal rod photoreceptor mosaic.[3] In follow-up of patients with AMN, persistent damage to the cone photoreceptor mosaic was documented at least one year after diagnosis, but some patients reported return of visual function despite documented abnormalities of cone structure.[4,5] Similar reports of function within areas of structural damage have been documented with other maculopathies, including macular telangiectasia type 2[6].

The objective of our study is to characterize foveal function in areas of apparent structural damage, which may provide insight into the relationship between structure and function given current technological advances in imaging.

2. Materials and methods

A patient presented after a viral illness with bilateral vision loss, mild vitritis, and SD-OCT and AOSLO images suggestive of focal cone loss at the fovea, findings diagnosed clinically as acute, bilateral foveolitis.

Informed consent was obtained after the study protocol and its associated risks were reviewed with the subject. The informed consent forms and study protocol were approved by the University of California San Francisco and University of California Berkeley Institutional Review Boards. The patient consented to publication of the findings of this study in writing. The patient was imaged 1 and 5 years after the initial diagnosis, but fundus-referenced tests of visual function were measured only at 5 years after symptom onset. The eye with better vision was chosen as the study eye based on visual acuity, fixation stability and AOSLO image quality.

2.1. Structural imaging

Complete eye examination including best-corrected visual acuity, color fundus photographs (Topcon 50EX, fundus camera, Topcon Medical Systems, Oakland, NJ), and infrared reflectance images (Spectralis HRA + OCT system [Heidelberg Engineering, Vista, CA, USA]) were completed after the study eye was dilated with one drop each of 1% tropicamide and 2.5% phenylephrine. SD-OCT b-scan images were obtained at 1° intervals through the central 20°, including the foveal avascular zone, at each visit. Horizontal SD-OCT scans through the PRL were exported to data analysis software (Igor Pro; WaveMetrics, Inc., Portland, OR) and manually segmented using sub-routines[7–11] to identify boundaries between the different retinal layers. Thickness of the outer nuclear layer at the fovea at visits 1 and 5 years after symptom onset was compared to measures from 20 normal subjects (mean age 45, standard deviation 10.2). Fundus-guided microperimetry (Nidek MP1, Nidek, Fremont, CA, USA) was measured in each eye 1 year after symptom onset in a light adapted state using a Goldmann III stimulus for 200 msec and 4–2 threshold strategy. The patient was asked to look in the center of 4 crosses, each 2° in size, located at 20° eccentricity around fixation.

Directional-OCT (D-OCT) was performed using an SD-OCT system with eye tracking on loan from Carl Zeiss Meditec (prototype). D-OCT is a technique whereby OCT images of the same structure are taken with three different illumination angles and analyzed using an approach that reveals the presence of structures in the retina with directional reflective properties. The full technique is described in other papers.[12,13] The purpose of the D-OCT measurements in this study was to look at the directionally-reflective properties of the waveguiding cone photoreceptors[14] and to explore the possibility of the presence of misdirected cones in the lesion of the patient.

A custom-built AOSLO system was used to obtain high-resolution images of the study eye as previously described.[15–17] AOSLO videos covering 1.2° × 1.2° of retina were processed to produce stabilized images that were assembled into montages which included the anatomic fovea, the macular area with IS/OS junction band disruption, and surrounding normal cones in the subject's eye.

2.2. Functional testing

Fundus-referenced visual testing was performed, including identification of the preferred retinal locus (PRL), an AOSLO-administered letter discrimination task, and fundus-guided microperimetry using a tracking SLO (TSLO). The method of identifying the PRL is described in a previous paper.[18] Areas identified by the SD-OCT images and AOSLO montages that suggested photoreceptor loss were specifically tested with the AOSLO discrimination task and with TSLO microperimetry.

2.2.1. AOSLO discrimination

An AOSLO-corrected discrimination task was performed to test visual function in and around the lesion. The test was a four-alternative-forced-choice tumbling 'E' task, where the letter E was directly projected onto the retina by modulating the 840 nm source in the AOSLO raster scan.[19] To the subject, the letter appeared as black on a dim (~4 cd/m^2) red background. The letter size was greater than the minimum threshold measured clinically (Snellen equivalent of 20/30) and was presented 125 times for a duration of one second on each trial (30 video frames). An AOSLO video was recorded for each trial, along with the subject responses. Since the stimulus was delivered by modulating the imaging beam, the stimulus was encoded directly into the video. As such, the exact location of the stimulus over the course of each 1-second trial was recorded. The analysis of the results was focused on those trials that remained within the lesion for the entire 1-second duration.

2.2.2. Fundus-guided microperimetry

The TSLO is a custom-built system that was modified to perform similar fundus-guided microperimetry testing as has been described for the AOSLO.[6,20] In both systems, accurate fundus-guided microperimetry is achieved via real-time, high-speed,