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Selective Cone Photoreceptor Injury in Acute Macular Neuroretinopathy

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Abstract

Purpose—To evaluate retinal structural and functional abnormalities in a patient with Acute Macular Neuroretinopathy (AMN).

Methods—An adaptive optics scanning light ophthalmoscope (AOSLO) was used to image the photoreceptor mosaic and assess rod and cone structure. Spectral domain optical coherence tomography (SD-OCT) was used to examine retinal lamination. Microperimetry was used to assess function across the macula.

Results—Microperimetry showed reduced function of localized areas within retinal lesions corresponding to subjective scotomas. SD-OCT imaging revealed attenuation of two outer retinal bands typically thought to reflect photoreceptor structure. AOSLO images of the photoreceptor mosaic revealed a heterogeneous presentation within these lesions. There were areas containing non-waveguiding cones and other areas of decreased cone density where the remaining rods had expanded to fill in the vacant space. Within these lesions, cone densities were shown to be significantly lower than eccentricity matched areas of normal retina, as well as accepted histological measurements. A 6-month follow up revealed no change in rod or cone structure.

Conclusions—Imaging of AMN using an AOSLO shows a preferential disruption of cone photoreceptor structure within the region of decreased retinal sensitivity (as measured by microperimetry). AO-based imaging tools provide a noninvasive way to assess photoreceptor structure at a level of detail that is not resolved by use of conventional SD-OCT or other clinical measures.

Keywords

Acute Macular Neuroretinopathy; Adaptive Optics; Cones; Macula; Optical Coherence Tomography; Photoreceptors; Retinal Imaging

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Introduction

First described by Bos and Deutman¹, acute macular neuroretinopathy (AMN) is a rare condition that typically affects young females. Clinical presentation includes sudden onset paracentral scotomas with dark, wedge-shaped parafoveal lesions.¹ It is often preceded by flu-like symptoms, though it has also been associated with oral contraceptives, contrast media, epinephrine, trauma, history of headache or migraine headache, postpartum hypotension, and hypotensive shock.² Despite numerous investigations, the exact etiology remains unclear. While initially described as a condition affecting the inner retina, hence the name, reports analyzing early receptor potentials, optical coherence tomography (OCT) and multifocal electroretinography (mfERG) have localized structural and functional abnormalities to the outer retina.³⁻¹⁹ Among the reports utilizing OCT, there is variation regarding which regions of the outer retina are reported to be involved. There are reports of photoreceptor inner segment/outer segment (IS/OS) junction defects,^{6-8, 10, 12, 13, 15} thinning of the outer nuclear layer (ONL),^{6, 7, 13, 15, 20} thinning of the photoreceptor outer segments,¹⁵ and a localized hyperreflectivity in the outer retina, which was later replaced by degenerative changes on follow-up.^{3, 8, 20, 21} The earliest OCT findings in the disease progression have shown hyperreflectivity of the posterior border of the outer plexiform layer at 3 hours after initial symptoms, which disappeared and was replaced by loss of the IS/OS border and thinning of the ONL at 1-week follow-up.²² There are no histopathologic data available to identify the exact site of injury in AMN.

While OCT provides good axial resolution, its lateral resolution is limited due to the eye's monochromatic aberrations. Adaptive optics (AO) imaging systems correct for these aberrations, enabling high-resolution visualization of individual cone and rod photoreceptors.^{23, 24} There are a growing number of cases where these two imaging modalities are used to provide complementary information about the structure of the outer retina.²⁵⁻²⁸ In some cases, photoreceptor abnormalities are visible using AO imaging tools but not with OCT.²⁹⁻³¹ As such, AO imaging may be useful in elucidating photoreceptor structure in AMN and other conditions. Here, we used an adaptive optics scanning light ophthalmoscope (AOSLO) to image a young female patient diagnosed with AMN, demonstrating a selective loss of cone photoreceptors. Registration of the images of the photoreceptor mosaic with those from other diagnostic modalities confirmed the photoreceptor injury localized to the scotoma seen with microperimetry, and the area of outer retinal disruption observed with SD-OCT.

Methods

Human Subject

The research was approved by the Institutional Review Board at the Medical College of Wisconsin and followed the tenets of the Declaration of Helsinki. Informed consent was obtained from the patient after explanation of the nature and possible consequences of the study. For all imaging modalities, the left eye was dilated and accommodation suspended using one drop each of Phenylephrine Hydrochloride (2.5%) and Tropicamide (1%).

Optical Coherence Tomography Imaging

Volumetric images of the macula were obtained with a Cirrus HD-OCT (Carl Zeiss Meditec, Dublin, CA). Volumes were nominally 6×6 mm and consisted of 128 B-scans (512 A-scans/B-scan), acquired at 27,000 A-scans/second. The internal fixation target of the system was used, which is a large green asterisk on a red background. Retinal thickness was calculated using the built-in macular analysis software of the Cirrus (ver. 6.0), which is automatically determined by taking the difference between the ILM and RPE boundaries. Volume scans were manually examined for segmentation errors, and there was no evidence of segmentation error in any of the scans. For each macular volume, a 50 μ m slab based on the contour of the RPE was formed and centered on the OS/RPE band. A summed volume intensity projection (VIP) was then created from this slab for enhanced visualization of outer retinal disruptions.

Additional images of the macula were obtained using a Bioptigen SD-OCT (Bioptigen, Inc., Durham, NC). Line scan sets were acquired (1000 A-scans/B-scan; 100 repeated B-scans) at the foveal center, and this location was confirmed based on inspection of an additional high-density volume scan. Scans were acquired through the pupil center. Scans were registered and averaged to increase signal to noise ratio, as previously described.³² The volumetric scans (1000 A-scans/B-scan, 100 B-scans/volume) provided dense sampling throughout the macula, enabling more precise comparison between SD-OCT findings and those from other modalities. To examine reflectivity of the outer retinal layers, longitudinal reflectivity profiles (LRP) were constructed as previously described.^{33, 34}

Imaging the Photoreceptor Mosaic

An AOSLO was used to image the photoreceptor mosaic across the area corresponding to the functional defects as well as adjacent, normally-functioning areas. Full system details can be found elsewhere.^{35, 36} A 680 nm superluminescent diode was used for reflectance retinal imaging, with the field of view of each image subtending about $0.96^\circ \times 0.96^\circ$. The patient was instructed to fixate at different positions to allow imaging of different retinal locations. Individual image sequences contained 150 frames, which were processed and averaged as outlined below.

Processing of AOSLO image sequences—In order to correct for distortions in the retinal images due to the sinusoidal motion of the resonant optical scanner, we first estimated the distortion from images of a Ronchi ruling, and then re-sampled the images over a grid of equally spaced pixels. After this “desinusoiding”, the movies were manually

inspected to identify reference frame(s) with minimal distortion and maximal sharpness for subsequent registration using custom software.³⁷ Registration of frames within a given image sequence was performed using a “strip” registration method, in which the images were registered by dividing the image of interest into strips, aligning each strip to the location in the reference frame that maximizes the normalized cross correlation between them.³⁷ Once all the frames were registered, the 40 frames with the highest normalized cross correlation to the reference frame were averaged, in order to generate a final image with an increased signal to noise ratio for subsequent analysis. The final images were then montaged using commercial software (Adobe Photoshop; Adobe Systems, San Jose, CA), and the final montage was manually registered to the color fundus image using alignment of blood vessels. Registration of images from different imaging sessions (6 months apart) was done using a coarse alignment procedure (i2K Retina, Dual Align, Clifton Park, NY), followed by the same strip registration described above.³⁶

Analyzing the cone mosaic—An area of $96\ \mu\text{m} \times 96\ \mu\text{m}$ from four different locations within the large AOSLO montage was cropped and used for subsequent analysis of photoreceptor density. The locations were chosen to represent areas with distinct photoreceptor structure, and were larger than typically used owing to the heterogeneous appearance of the mosaic. A previously described semi-automated algorithm was used to identify the rods in the images.³⁸ Being fewer in number and often more irregular, cones in the same cropped images were then manually selected using ImageJ (National Institutes of Health, Bethesda, MA).

Microperimetry

Microperimetry testing was obtained using an OPKO/OTI microperimeter (OPKO Instrumentation, Miami, FL). The protocol previously described by Anastakis *et al.* was followed to obtain retinal sensitivity measurements.³⁹ This involved using the Polar 3 testing pattern, which includes 28 points arranged in three concentric circles (2.3° , 6.6° , and 11° in diameter). Additional points were added manually to more finely sample affected areas. The stimulus was equal to the size of the Goldman III, with a 200 ms duration of presentation and 1.5 s interval between each stimulus presentation.

Results

The patient was a 26-year-old woman with a 1-month history of paracentral scotomas temporal to fixation in her left eye. The subjective size and character of the scotomas had been constant since onset. The onset of symptoms was preceded by flu-like symptoms, otherwise she was in excellent health. She was taking ethinyl estradiol and norgestimate (TriNessa) and loratadine (Claritin). Visual acuity with minimal myopic correction was 20/20 in each eye. With Amsler grid testing, she drew 2 small scotomas just temporal to fixation in the left eye. Ocular media were clear with no cells in the anterior chamber of vitreous. The posterior segment of the right eye was normal. The macula of the left eye had slightly dull foveal reflex (Fig. 1a). Intravenous fluorescein angiography with transits in the left eye was normal.

Multiple modalities helped localize the specific retinal areas affected. Microperimetry demonstrated areas of decreased sensitivity, corresponding to the areas of affected retina (Fig. 1b). Interestingly, the infrared SLO image acquired during the microperimetry protocol identifies two hyporeflective areas that align with the functional deficits (Fig. 1b), consistent with previous reports.^{7, 12, 13, 20} These two hyporeflective areas were also visible in the summed VIP derived from the Cirrus macular volume scan (Fig. 1c). As the VIP is comprised of a 50 μm slab approximately centered on the OS/RPE band this supports the idea that the hyporeflectivity observed in the IR image (Fig. 1b) is due to a disruption in melanin reflectance.²⁰ Consistent with this, inspection of a high-resolution SD-OCT line scan through the nasal lesion (Fig. 1e) shows severe disruption of the third band in the outer retina, which is thought to correspond to the contact cylinder of the cones, or the “OS/RPE”.⁴⁰ In addition, there was attenuation of the second band, which is thought to originate from either the ellipsoid portion of the inner segment (ISe),^{40, 41} or the inner segment/outer segment junction (IS/OS).⁴² Qualitatively, there were no other abnormalities in the remaining retinal layers, including the choroid and retinal pigment epithelium (RPE). Compared to unaffected retina, an LRP analysis within the lesion demonstrated a 1.8-fold reduction in ISe intensity and a 2.5-fold reduction in OS/RPE intensity (Fig. 2).

We acquired an extensive montage of the photoreceptor mosaic using the AOSLO, encompassing both parafoveal lesions and a large region of unaffected retina (Fig. 1d). Normally, rods and cones appear as bright spots in such images due to their waveguide properties; light is directed into the photoreceptor, where it is then reflected and guided back out of the photoreceptor towards the pupil center.⁴³ We observed focal areas of non-waveguiding cones within the lesion, with apparent preservation of the rod mosaic. An example of this is shown in Figure 3, with an image from an age- and gender-matched normal retina shown for comparison. Cone density in this image from within the lesion is 5,667 cones/ mm^2 , compared to 13,178 cones/ mm^2 for the normal retina. Previous in vivo estimates of cone density at a similar eccentricity revealed a range of 12,257 – 17,766 cones/ mm^2 .²⁴ Rod density in this image from within the lesion is 84,342 rods/ mm^2 , compared to 93,595 rods/ mm^2 for the normal. Previous in vivo estimates of rod density at a similar eccentricity revealed a range of 71,373 – 110,619 rods/ mm^2 .²⁴

The montage of the photoreceptor mosaic was aligned to the SD-OCT image to compare the visualization of these outer retinal defects (Fig. 4). The areas of the montage with the non-waveguiding cones correlated with the disruption of the outer retinal bands on the SD-OCT image (attenuation of the inner segment ellipsoid band and decreased reflectivity of the cone contact cylinder band). Temporal to the area of non-waveguiding cones, we observed a focal reduction in the intensity and clarity of the photoreceptor mosaic. Interestingly, the photoreceptor mosaic displayed variable appearance. Within the paracentral lesions, the two distinct patterns of photoreceptor structure were seen (Fig. 5). Abnormal areas displayed either the pattern of nonwaveguiding cones described above, or a pattern of decreased cone density within a contiguous rod mosaic. Retinal areas outside of the lesions displayed expected cone and rod structure (Fig. 5), and foveal cone density was within normal limits (109,500 cones/ mm^2). No photoreceptor disruption was seen outside the visible lesions, indicating good agreement between the disruptions on SD-OCT and that seen on AO.

The same retinal areas were imaged using the AOSLO at two separate time points, approximately 6 months apart (Fig. 5). Precise alignment of images from the same retinal location allowed for assessment of cellular changes over this time period. Specifically, we were interested to see whether or not the non-waveguiding cones might progress to a pattern more similar to the other area of affected retina due to further degeneration of those non-waveguiding cones. However, we did not observe a significant change in rod or cone density across the two imaging sessions, at any of the locations analyzed. For an area containing non-waveguiding cones (1.3mm from the fovea), the cone density was calculated to be 7,744 cones/mm² and 7,636 cones/mm² at the two time points, respectively. For this same area, the rod density was calculated to be 59,799 rods/mm² and 58,616 rods/mm² at the two time points, respectively.

In another abnormal area (1.9mm from the fovea), the cone density was reduced and calculated to be 6,130 cones/mm² and 6,022 cones/mm² at the two time points, respectively. The rod density was calculated to be 84,536 rods/mm² and 85,504 rods/mm². An unaffected area of her retina (1.9mm from the fovea) had a cone density of 14,519 cones/mm² and 14,197 cones/mm² at the two time points, respectively. The rod density was 76,147 rods/mm² and 81,094 rods/mm² in this unaffected area at the two time points, respectively.

Discussion

The application of multiple imaging modalities in assessing AMN has shown to be useful in clarifying the structural changes in the retina that occur in this rare condition. Our results agree with previous reports localizing the defects to the outer retina.^{12, 13, 15, 19} Distinct from previous reports, the use of an AOSLO to visualize the photoreceptor structure has allowed unique findings that have not been previously reported. We have shown there is a selective injury of cone photoreceptors within the lesions of AMN with rods apparently remaining unaffected. This cone disruption correlates with the decreased retinal sensitivity as assessed with microperimetry.

On SD-OCT we observed the emergence of the Henle fiber layer (HFL) in areas overlying the visible lesions (arrows, Fig. 4). While the HFL is sometimes visible in normal retinas, inspection of the macular volume showed that the enhanced visibility of the HFL in this patient was uniquely restricted to the retinal lesions in this patient. Nevertheless, one of the early findings in AMN is increased reflectivity within the ONL+HFL layer,^{3, 8, 20, 21} indicating that there may be direct damage to or inflammation of the HFL that increases its visibility.

Using an AOSLO, we observed remarkable heterogeneity of the photoreceptor structure within the lesions associated with this condition. Such fine discrimination of the microarchitecture of the lesions was not accessible with SD-OCT or the other clinical diagnostic tools. Of particular interest are the areas with reduced cone density and where the rods have rearranged to form a complete, contiguous mosaic. This is reminiscent of the findings of Curcio *et al.*, who showed that rods will expand to fill in vacated space produced by degeneration of neighboring rods in the aging retina.⁴⁴ In contrast to reports that AMN lesions resolve completely,^{10, 13} our data suggest that at least in some lesions, the

photoreceptor damage is not reversible. Conversely, other areas had dark spaces that were likely non-waveguiding cones. A similar appearance of cones was previously observed in individuals with red-green color blindness,²⁹ and it was shown using adaptive-optics microperimetry that these non-waveguiding cones were non-functional.⁴⁵ Similar non-waveguiding cone structure is also seen in patients with achromatopsia.⁴⁶⁻⁴⁸

These findings describing the photoreceptor structure are novel and valuable, seeing that no histopathologic studies have been reported on AMN. Our AOSLO data, together with previous SD-OCT findings showing persistent thinning of the ONL in AMN,²⁰ indicate that there is permanent loss of cone photoreceptors in this condition. In addition, it remains unclear whether the heterogeneous photoreceptor patterns within the lesions represent different degrees of injury or whether they are the lesions at different stages of the disease process. While our follow-up at 6 months did not show any significant structural changes, additional longitudinal imaging is required to fully understand the natural progression of the disease, especially if observation is begun when symptoms first occur.²² Regardless, our findings support the idea that the name AMN does not accurately reflect the disease origin, with the suggested acute macular outer retinopathy^{7, 15} providing a more accurate description of the disease.

A limitation of the current study is that we examined a single patient, as such, evaluation of more patients could shed light on the inter-lesion variability in our patient, increase the generalizability of our findings, and provide greater insight into the effects of AMN on macular photoreceptors. Nevertheless, this report provides a clear example of how high-resolution imaging with AO imaging tools can help clarify and detect structural changes in the retina that are not visible with current clinical imaging tools. With continued understanding of how photoreceptor structure relates to SD-OCT findings, AO imaging tools can enable better interpretation of SD-OCT disruptions of the outer hyperreflective layers, though additional studies like this in patients with variable rod and cone degeneration are needed.

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Summary

Adaptive optics imaging of Acute Macular Neuroretinopathy shows a preferential injury to cone photoreceptors within characteristic parafoveal lesions. Adaptive optics imaging provides a noninvasive assessment of photoreceptor structure undetectable with current clinical imaging modalities.

Figure 1.

Multiple imaging modalities localizing lesions in a patient with AMN. **a**, Color fundus photography demonstrating a slightly dull foveal reflex. **b**, Microperimetry showing reduced sensitivity corresponding to two hyporeflective areas detected on the SLO image. **c**, Summed volume intensity projection image constructed from a Cirrus macular volume scan, demonstrating two areas of disruption nasal to the fovea. **d**, Total area of photoreceptor mosaic imaged with the AOSLO, which covers both parafoveal lesions. Black line depicts location of corresponding optical coherence tomography image (e). **e**, Bioptigen SD-OCT high-resolution line scan shows disruption of the second and third bands. Vertical arrows indicate the location of the longitudinal reflectivity profiles shown in Figure 2.

Figure 2.

Assessing reflectivity of the ISe and OS/RPE bands in AMN. Shown on the left is a longitudinal reflectivity profile (LRP) acquired nasal to the fovea, at the location of the left arrow in Figure 1e. On the right is an LRP acquired at a comparable eccentricity in the temporal retina, at the location of the right arrow in Figure 1e. The LRP's were generated using a linear display of the SD-OCT data, to enable comparison of layer intensity. While the outermost band (labeled "RPE") was the same at the two locations, we observed a 1.8-fold reduction in the intensity of the ISe (or IS/OS) band and a 2.5-fold reduction in the intensity of the OS/RPE band within the lesion. (a.u.= arbitrary units)

Figure 3.

Images of the photoreceptor mosaic obtained at approximately 5 degrees from fixation in a normal control (**a**) as well as from within a lesion in the AMN patient (**b**). The same respective images are shown in a logarithmic scale, enhancing visualization of photoreceptor cells (**c,d**). Numerous non-waveguiding cones can be identified in the AMN patient, though the rod mosaic remains intact. Scale bar is 20 μm .

Figure 4. Correlating SD-OCT and AOSLO findings in AMN. **a**, SD-OCT image shows attenuation of the inner segment ellipsoid band and decreased reflectivity of the cone contact cylinder band. Arrows depict abnormally bright Henle fiber layer. **b**, AOSLO image corresponding to SD-OCT image. **c**, Enlarged AOSLO image shows photoreceptor disruption within and beyond the affected area visible with SD-OCT. Selective disruption of normal cone waveguiding properties is shown. Scale bar is 200 μm .

Figure 5.

Images of distinct patterns of photoreceptor structure found within a single paracentral lesion compared to a normal area of retina in the same patient, taken at two different imaging sessions. Approximately six months separate the top and bottom images of each respective location. The left column of images shows a pattern of non-waveguiding cones interspersed between normal-appearing cones and rods (1.3 mm nasal from the fovea), whereas the middle column of images shows a pattern of decreased cone density separated by a contiguous rod mosaic (1.9 mm nasal from the fovea). At 1.9 mm nasal and slightly inferior from the fovea, the unaffected area shows normal cone and rod structure. Aside from slight reflective intensity variations between individual cones and rods, there are no remarkable differences in the structure of the photoreceptor mosaic between the two time points. Scale bar is 50 μ m.