A Photographer Working in Black and White

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Introduction:

A 64-year-old woman was referred for complaint of photopsias in her right eye. She reported a history of long-standing poor central vision and deficient color vision. Her past medical history included prior orthopedic surgery and a mood disorder for which she took several psychotropic medications. She reported a brother with visual deficiencies similar to her own.

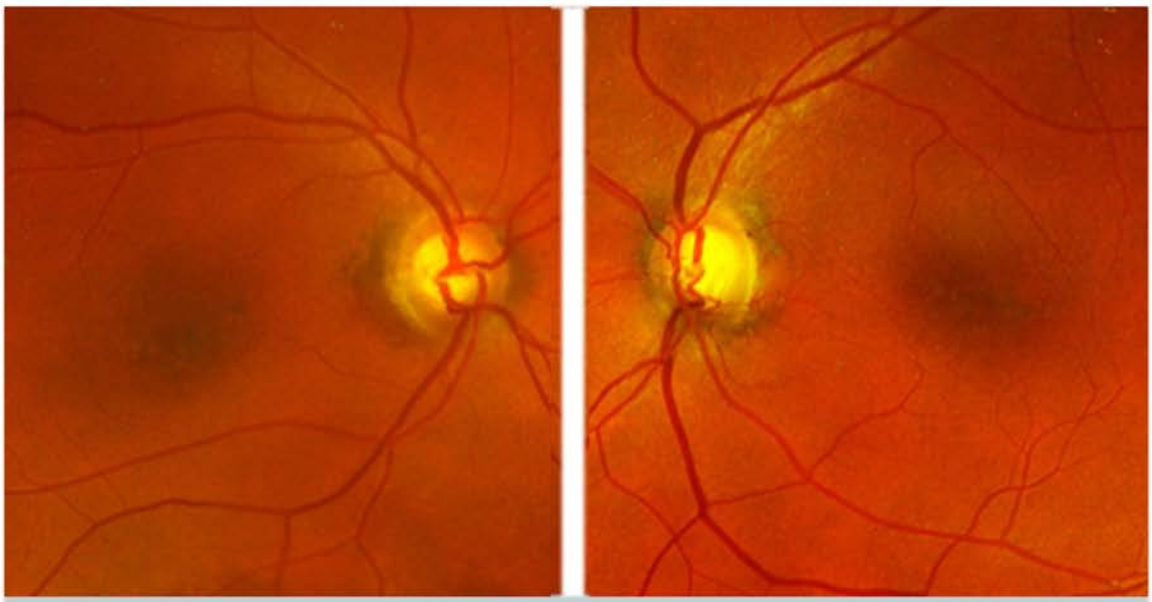

Figure 1. False-color fundus images demonstrate the central macular pigmentary changes in both eyes.

On exam her best-corrected visual acuity was 20/400 in both eyes. Motility examination revealed a small-angle exotropia; no nystagmus was present. Anterior segment examination was unremarkable and her intraocular pressures were 15 in both eyes. Fundus examination (Figure 1) revealed a large cup-to-disc ratio in both eyes without any focal thinning. Prominent pigmentary changes were present in the central maculae. Careful peripheral examination with scleral depression was unremarkable.

Fundus autofluorescence (Figure 2) demonstrated central hypoautofluorescence in the area of the macular pigmentary changes, with a surrounding ring of faint hyperautofluorescence, giving the appearance of a bull's eye lesion—particularly in the left eye. OCT (Figure 3) revealed outer retinal loss throughout both foveae. In the right eye an optically empty space was seen in an area of ellipsoid zone loss, and in the left eye the fovea appeared thinned and collapsed over an area of ellipsoid zone loss. In both eyes there was increased signal transmission through the attenuated retinal pigment epithelium beneath the foveae.

The patient elected to proceed with genetic testing, which revealed a homozygous pathologic variant of the CNGB3 gene, consistent with autosomal recessive achromatopsia. She was counseled on these findings and connected with low vision services. Despite her poor visual acuity the patient professed a passion for photography, and hoped to find ways to continue to this hobby in the future.

Discussion:

Achromatopsia is a rare autosomal recessive condition that results in loss of cone function. With a prevalence of approximately 1 in 30,000, achromatopsia often presents in early childhood with poor visual acuity (near 20/200), pendular nystagmus, photophobia, and hemeralopia—the latter describing "day blindness", or reduced visual acuity in bright light as compared to dim light.[1] In addition to nystagmus, young patients are often identified by high hyperopia and a paradoxical pupillary response. Fundus examination is

unremarkable in young achromatopes, but later in life macular pigmentary changes and RPE atrophy often develop. Electroretinography routinely proves diagnostic, with absent cone responses and normal rod responses.

An OCT staging system has been proposed for achromatopsia, and our patient demonstrates some of the key stages of the system.[2] The stages progress from a normal outer retinal appearance to the development of ellipsoid zone loss. Next is the appearance of an optically empty space in the outer retina—as seen in our patient's right eye—followed by partial RPE disruption. This empty space is thought to correspond the loss of foveal photoreceptor outer segments and is seen in several other macular dystrophies. The final OCT stage features outer nuclear layer loss with or without complete RPE disruption.

Five genes have thus far been implicated in the pathogenesis of achromatopsia, all related to the phototransduction cascade in cone cells. Mutations in the CNGA3 and CNGB3 genes—responsible approximately 80% of all cases of achromatopsia—affect subunits of a cGMP-gated cation channel in cone cells. There is significant documented heterogeneity in the mutations that can occur in these two genes, leading to incomplete achromatopsia in a minority of cases, where some residual color vision exists and visual acuity is marginally better than complete achromatopsia.[1]

Achromatopsia has become a notable target for gene therapy. After promising results in several animal models (canine, murine, sheep), clinical trials are underway investigating subretinal injection of a recombinant adeno-associated virus vector targeting the CNGA3 and CNGB3 mutations. Fisher et al. recently published results of safety and dose-escalation trials for the CNGA3 gene therapy. No substantial safety issues were present at 12-month follow up and all treated eyes (9 in total) demonstrated some level of improvement, with a mean visual acuity gain of 2.9 letters and a mean increase in contrast sensitivity.[3] Recruitment remains open in several trials for patients with CNGA3 and CNGB3 mutations.

Despite the promise of gene therapy, care for achromatopes usually centers upon controlling debilitating hemeralopia and photophobia. Tinted glasses and contact lenses, while not offering significant improvements in visual acuity, can improve patients' ability to function in the daytime.[4] Low vision services are all essential for achromatopes.

No discussion of achromatopsia is complete, from a literary standpoint, without mention of Oliver Sacks' work, The Island of the Colorblind.[5] In the 1996 book Sacks recounts his travels to the small atoll of Pingelap in the Federated States of Micronesia, where the prevalence of achromatopsia is an astounding 1 in 12. In 1775 a powerful storm—Typhoon Lengkieki—descended upon the atoll and killed an estimated ninety percent of the population. Among the few survivors was the nahnmwarki—the hereditary king of the island—who led the Pingelapese as they repopulated the atoll. Pedigree analysis would ultimately reveal that the nahnmwarki carried a CNGA3 mutation that proved critical in the prevalence of achromatopsia in the isolated island kingdom.

Travelling with a British ophthalmologist and a Danish achromatope, Sacks describes life on the small island—under one square mile—where squinting islanders affected with the "maskun" are easy to spot. Sacks finds achromatopes to be adept fishermen, and thus able to participate in the island's dominant economic endeavor. Yet under the tropical midday sun those with the maskun are often nowhere to be seen—taking shelter in

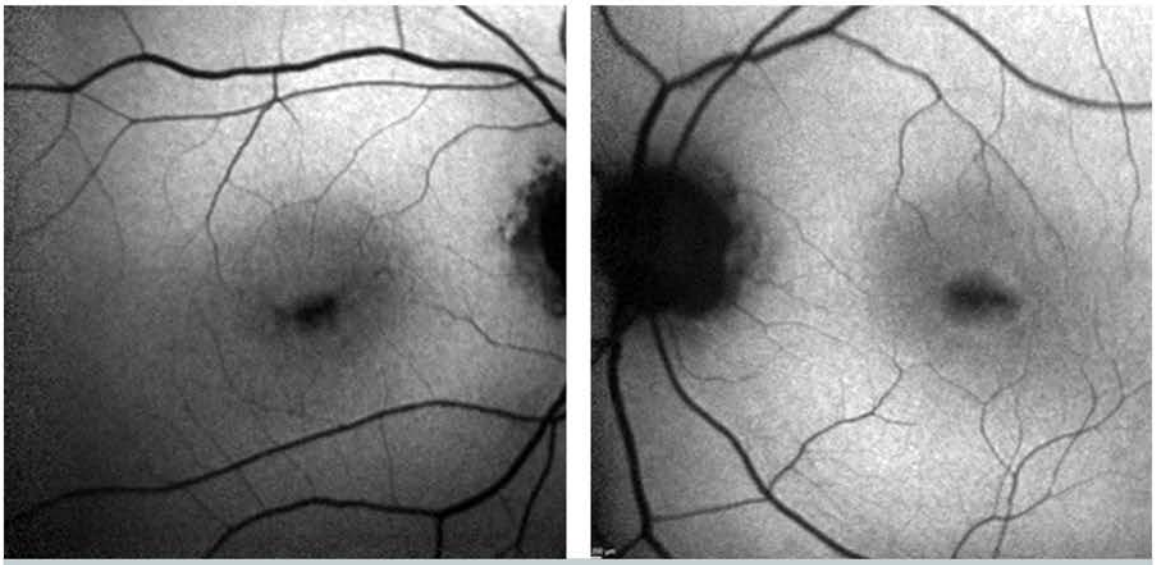

Figure 2. Fundus autofluorescence images with foveal hypoautofluorescence with a faint ring of hyperautofluorescence.

the shade of their rudimentary domiciles.

The Pingelapese have incorporated achromatopsia into the mythical history of their island. The maskun is at times explained as a result of the god Isoahpahu's affair with the wife of king Okonomwaun, and at other times as the curse of a spurned Christian missionary. Others on Pingelap see the maskun as a contamination from the outside world, brought back to the island by laborers forced to work in German phosphate mines on the island of Nauru. Sacks describes how this latter idea seemed to be reinforced during his visit by the presence of the Danish achromatope accompanying him—the first non-Pingelapese affected with the maskun the islanders had ever met.

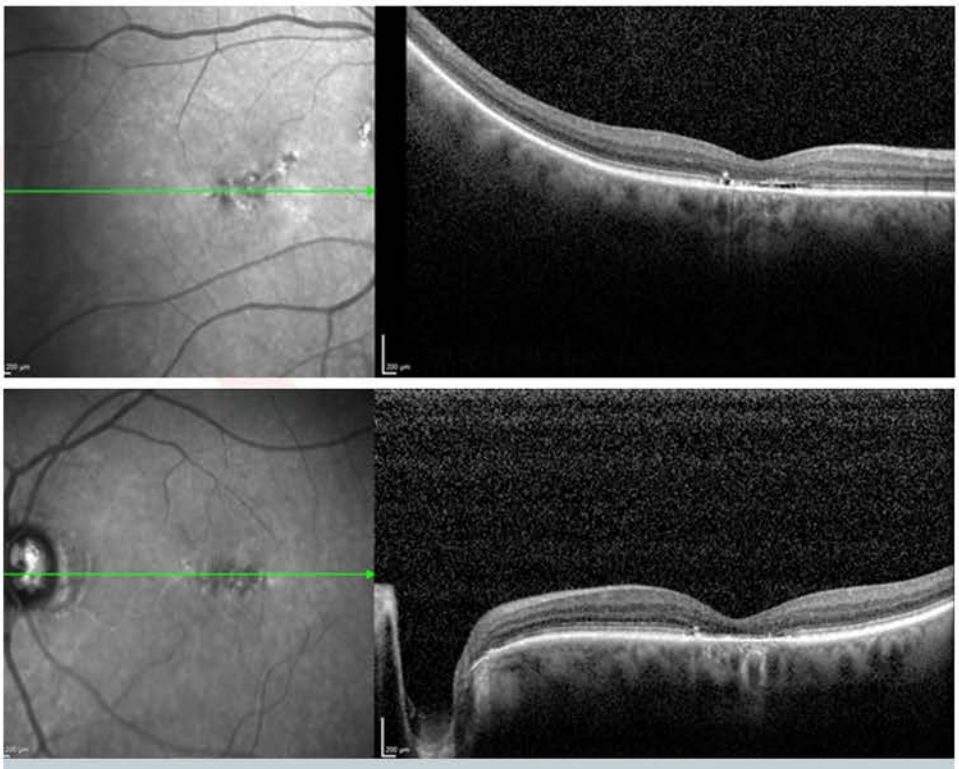

Figure 3. OCT images with ellipsoid zone loss and an optically empty zone in the right eye and more prominent outer retinal loss in the left eye. Both eyes demonstrate increased signal transmission through the attenuated subfoveal RPE.

Visiting the island before the advent of subretinal gene therapy, Sacks and his companions had little hope to offer the Pingelapese achromatopes. They handed out sunglasses—in one case calming the cries of a squinting baby on the spot—and shared stories and sympathies with the islanders. However the Pingelapese achromatopes needed little in the way of consolation; once identified by their wandering, squinting eyes as children, those with the maskun faced a life with challenges, but also a place in a community. The greatest effect of the visit was perhaps on the Danish achromatope, who for several days left behind the isolation of being 1 in 30,000 and found an abundance of unexpected fellowship on one of the most remote outposts in the vast Pacific.

References:

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