CONE DYSTROPHY IN 33-YEAR-OLD WOMAN

Consider the entire clinical picture while looking for subtle clues to arrive at the accurate diagnosis.

BY CHRISTOPHER J. BORGMAN, OD, FAAO

A 33-year-old Black female was referred to me by a colleague for a second opinion on progressive vision loss. The patient reported slowly worsening vision OU over 6 months that was worse in her left eye. She also reported worsening ability to perform activities of daily living, specifically at work, where she was having difficulty with computer work required by her employer. She denied any history of trauma, and both her and her family's ocular history was unremarkable.

Her medical history was positive for epilepsy, which was diagnosed 16 years earlier and being treated with oxcarbazepine. The patient had been following up with her neurologist at least every 6 months, and a brain MRI ordered approximately 3 months prior was normal/stable compared with previous MRI findings. She denied any medical allergies, and her social history was unremarkable. She was not able to drive an automobile due to seizure activity related to her epilepsy.

A CLOSER LOOK

The patient's BCVA was 20/70 OD and 20/40 OS with mild myopia (-1.50 SPH OD, -1.00 SPH OS). Her pupils were equal, round, and reactive to light without afferent pupillary defect. Confrontation visual fields showed central depressions bilaterally (OD > OS). Her IOP was 10 mm Hg OU as measured with the iCare IC100 tonometer (iCare). The external slit-lamp and dilated fundus examinations initially appeared unremarkable (Figure 1).

Because I couldn't find an obvious explanation for the patient's reduced visual acuity, the idea of nonorganic vision loss entered my differential diagnosis. However, I began spot-checking several areas of her eyes in an investigative pattern I often refer to as "going fishin'" with my students, by which I mean checking easily overlooked areas. This usually involves formal corneal topography, as I've been burned on keratoconus and irregular astigmatism more than once. The patient's corneal topography showed normal

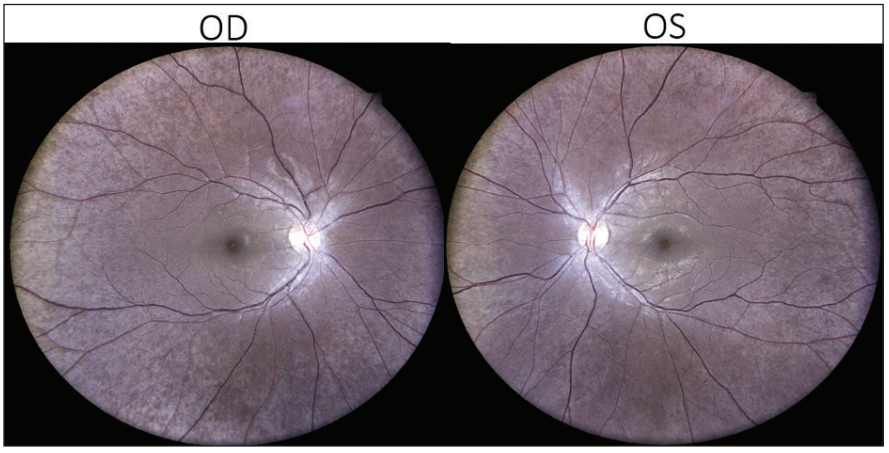


Figure 1. Color retinal photography of right and left eye did not reveal an immediate cause for concern.

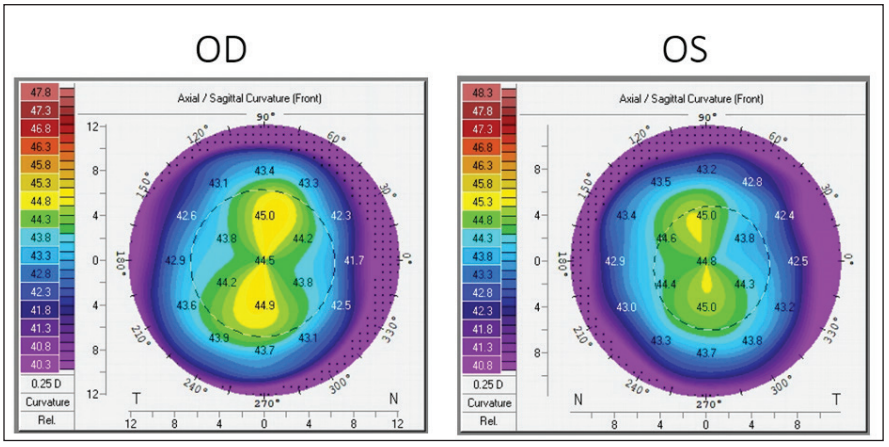


Figure 2. Corneal topography, axial/sagittal curvature, and anterior corneal surface of the right and left eye were normal.

with-the-rule bow-tie patterns bilaterally, which ruled out irregular astigmatism and keratoconus (Figure 2). OCT scans (Cirrus 5000, Zeiss) with retinal nerve fiber layer and ganglion cell analyses were also normal in each eye (Figure 3). Next, I obtained macular OCT scans (Spectralis, Heidelberg Engineering), which show better detail and higher resolution of the retinal layers in my experience, and these revealed irregular "shaggy and blurry" photoreceptor segments throughout the macula of each eye (Figure 4). Reflex fundus auto-fluorescence scans supported the high-resolution OCT, showing small areas of scattered hyper- and hypofluorescent macular areas (Figure 5), suggesting photoreceptor and/or retinal pigment epithelium involvement.

ColorDx CCT HD (Konan Medical) color vision testing showed reduced red and green wavelength color discrimination (OD > OS) (Figure 6). Formal visual field testing was performed, including both 24-2 and 10-2 protocols (Figures 7 and 8), which showed scattered depression points in the visual field OD and central scotomas in the visual field OS. Confident that cone photoreceptor dysfunction may be playing a role in this patient's progression vision loss, I ordered full-field electroretinography to compare rod and cone photoreceptor function. Rod photoreceptor function was normal (Figure 9), but cone photoreceptor function was reduced (Figure 10), supporting my suspicion of a cone dystrophy. Genetic testing was discussed with the patient to check for known cone dystrophy genetic mutations, and she consented to providing a buccal sample. Genetic testing revealed a positive mutation of the *ABCA4* gene associated with Stargardt macular dystrophy and cone-rod dystrophy.

DIAGNOSING INHERITED RETINAL DISEASES

Inherited diseases generally fall into one of two categories: stationary and progressive.[1] Stationary disorders are either congenital or early infantile onset, while progressive disorders usually develop later.[1] Molecular genetic testing has greatly

AT A GLANCE

- Irregularities in the photoreceptor layer with inherited retinal diseases (IRDs) are well-documented and align with the presentation of the photoreceptor layer details observed on OCT for this patient.
- Treatment for most IRDs is aimed at maximizing remaining vision with low vision aids, assistive technologies, and counseling services.
- Genetic testing can help with providing an accurate diagnosis and prognostic information, offering directed treatment options for IRDs, enrolling patients in research studies, and assessing reproductive risk.

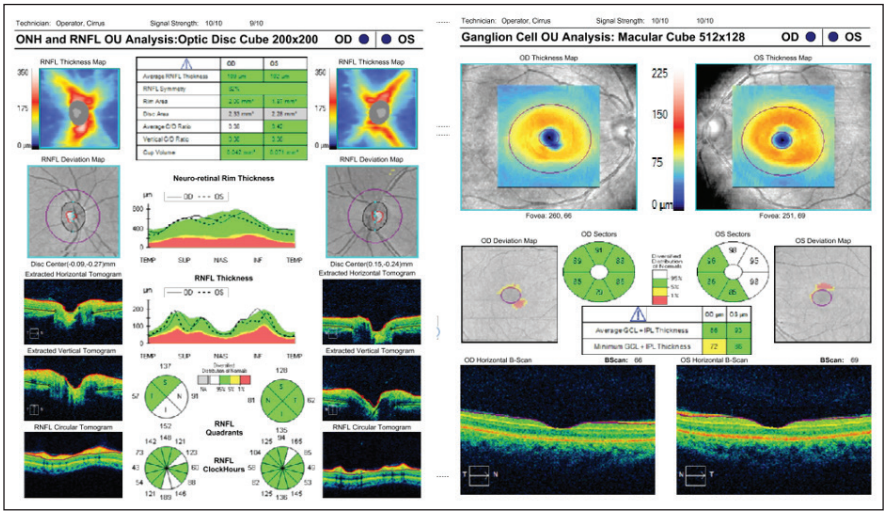


Figure 3. Cirrus OCT scans of each eye with retinal nerve fiber layer analysis (left) and ganglion cell analysis (right) were also normal.

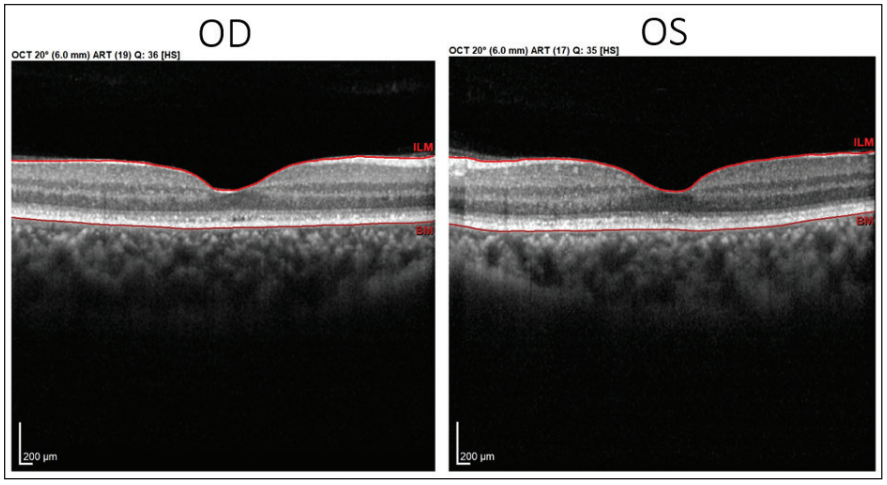


Figure 4. OCT of the right and left macula showed an irregular, poorly defined, and "shaggy/blurry" appearance of the photoreceptor layers in each eye.

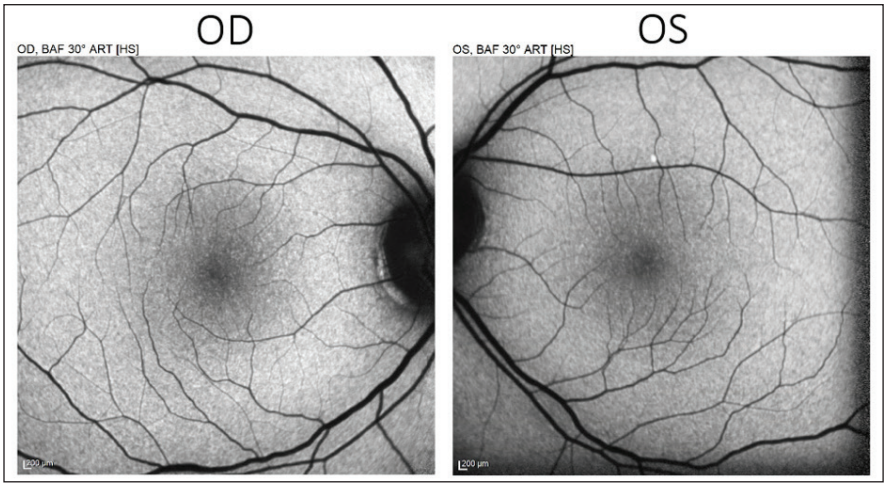


Figure 5. Fundus autofluorescence of the right and left posterior pole showed mild stippling of the macula of each eye.

increased the ability to detect pathogenic variants in patients suspected of having stationary or progressive hereditary eye diseases.[1]

Today, genetic testing is much more accessible and helps provide an accurate diagnosis and prognostic information, offer directed treatment options, enroll patients in possible research studies, and assess reproductive risk and counseling.[1] Beyond comprehensive eye examinations, there are many technologies to assist in helping diagnose and follow patients with an inherited disease.[2] It can be difficult to make specific diagnoses based on clinical examination alone; thus, further testing is extremely useful in determining the correct diagnosis.[3] Specifically, the following tests are valuable tools to make accurate diagnoses in inherited retinal diseases (IRDs): color fundus photography, fundus autofluorescence, spectral-domain OCT, visual field testing, adaptive optics, and electroretinography (full-field and multifocal).[2-9]

Loss of foveal cone structure has been shown to precede vision loss in patients with rod-cone dystrophies.[10] Irregularities in the photoreceptor layer in IRDs have been described previously,[9] and this fit well with the presentation of my patient's photoreceptor layer details on OCT. The irregular, "shaggy and blurry" nature of the photoreceptor layer is obvious on OCT testing when clinical observation skills are used to assess the retina.

MORE ON CONE DYSTROPHIES

Cone dysfunction syndromes are a collection of IRDs that affect cone photoreceptor function and are generally diagnosed based on clinical characteristics, additional testing, and molecular genetics.[11]

Inheritance

The mode of inheritance can be autosomal dominant, autosomal recessive, X-linked, or unsolved.[5] It

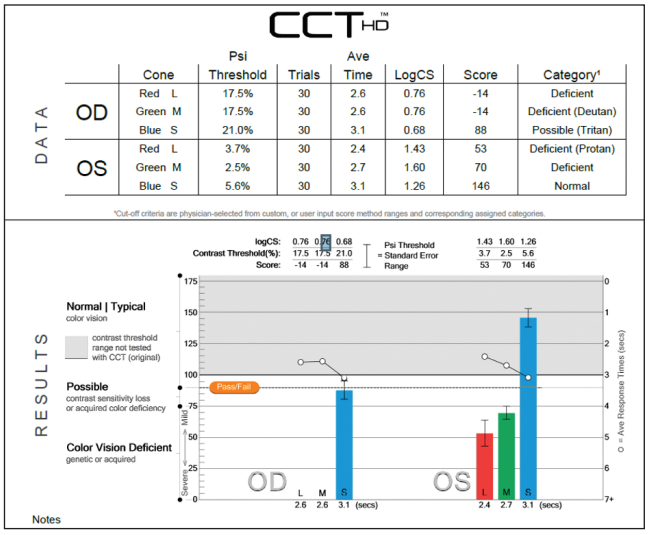


Figure 6. ColorDx color vision testing showed reduced red and green wavelength discrimination of the right and left eye. Note that the right eye appears worse than left, which correlates with other patient history and clinical exam findings.

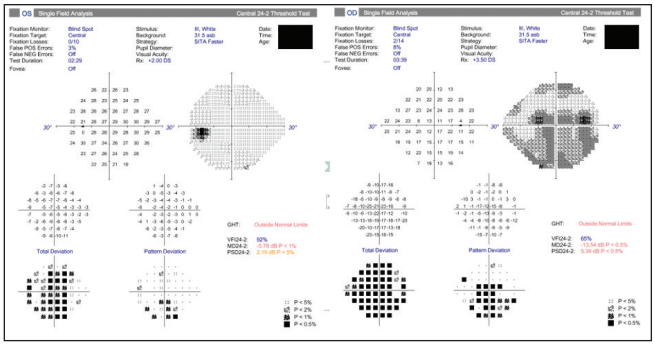


Figure 7. Humphrey visual field analyzer (24-2 protocol) showed mild inferior paracentral depression in the left eye and central scotoma/depression in the right eye.

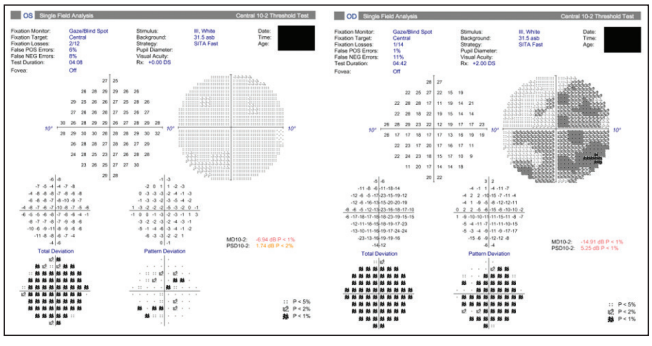


Figure 8. Humphrey visual field analyzer (10-2 protocol) showed mild scattered paracentral depressions in the left eye and central scotoma/depression in the right eye, correlating with other patient history and clinical exam findings.

would seem logical to think that autosomal dominant forms of cone and cone-rod dystrophies would be most common, as only one copy of the mutated gene needs to be present to cause disease. But surprisingly, a recent study by Gill et al showed that the two most common modes of inheritance are unsolved (43.7%) and autosomal

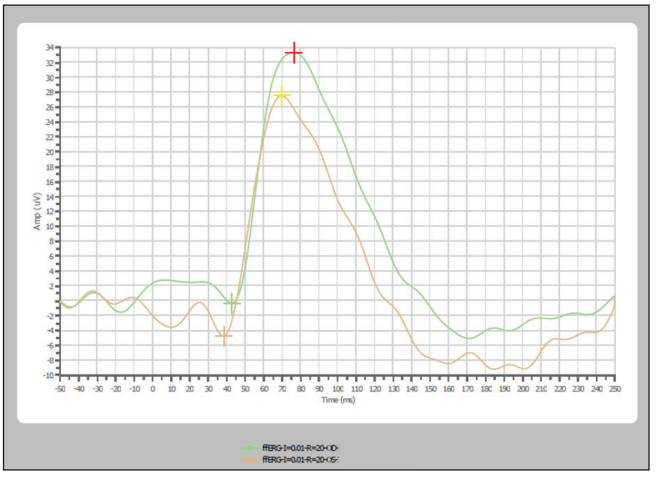
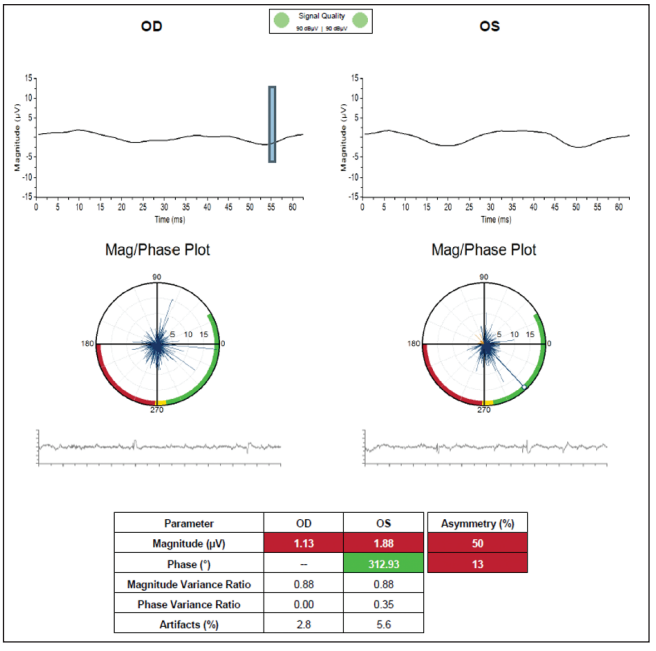


Figure 9. Full-field electroretinogram of the right (green recording) and left (orange recording) eyes. Note the normal waveforms, amplitudes, and timing in each eye, which suggests normal rod photoreceptor function.



Parameter	OD	OS	Asymmetry (%)
Magnitude (µV)	1.13	1.88	50
Phase (°)	--	312.93	13
Magnitude Variance Ratio	0.88	0.88	
Phase Variance Ratio	0.00	0.35	
Artifacts (%)	2.8	5.6	

Figure 10. Full-field electroretinogram and photopic flicker (32 Hz) of the right and left eyes showed essentially flat waveforms and poor/low signal amplitudes in each eye, which is suggestive of significant cone photoreceptor dysfunction.

recessive (43.2%), followed by autosomal dominant (12.2%) and X-linked (0.9%).[5] The most common autosomal recessive mutation occurs in the *ABCA4* gene (62.2%), which was the case with my patient, while the most common autosomal dominant mutation occurs in the *GUCY2D* gene (34.6%).[5] The most common X-linked mutation occurs in *RPGR* (73%).[5]

Treatment

Treatment for most inherited ocular diseases is supportive and aimed at maximizing remaining vision with low vision aids, assistive technologies, and counseling

services.[1] In my opinion, low vision services are often underused, so my threshold for referring to my low vision colleagues is extremely low after witnessing the amazing services they can offer patients experiencing vision loss. I discussed low vision consultation with this patient, and she was highly motivated to explore her options, so we scheduled her for the next available consultation.

ALWAYS LOOK TWICE—OR EVEN THREE TIMES

This case highlights the importance of using all available technologies to make the correct diagnosis—in this case, a cone dystrophy. Admittedly, and mildly embarrassingly, until I took a second look at the patient's OCT scans, I seriously considered nonorganic vision loss as the most likely diagnosis. But the collaborative advice from two mentors of mine, Leonard Messner, OD, FAAO, and Dennis Mathews, OD, rang loudly in my ears: "Before you blame the patient, take a second (or third) look at the entire clinical picture and make sure you, the doctor, are not missing a subtle clue."

In my experience, wiser words have never been spoken. Nonorganic vision loss is not a diagnosis of exclusion and must be supported by positive findings on examination that demonstrate normal visual function.[12] I hope this case helps you make more accurate and confident diagnoses with IRDs and avoid pitfalls, should you encounter a similar case. ■

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