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Use of Spectral Domain OCT to Visualize Photoreceptor Abnormalities in Cone/Rod Dystrophy-6

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Abstract

Purpose—To describe the spectral domain OCT (SD-OCT) findings in a patient with cone-rod dystrophy 6 (CORD6).

Method and Patient—Case report of a 13 year-old girl who presented with progressive loss of vision. Fundus photography, a fluorescein angiogram, an electroretinogram, autofluorescence imaging, SD-OCT, and genetic testing were performed.

Results—The patient's fundi showed mild granularity of the perifoveal retinal pigment epithelium. An electroretinogram demonstrated cone dysfunction and normal rod function. Genetic testing revealed a heterozygous CGC>CAC nucleotide substitution at codon 838 of the *GUCY2D* gene. This results in an amino acid change of Arg838His and provided a molecular diagnosis of CORD6. The SD-OCT showed abnormalities at the inner segment/outer segment junction and the outer segment layer, suggestive of loss or disease of photoreceptor outer segments. Autofluorescence imaging demonstrated a perifoveal ring of hyperfluorescence that correlated with abnormalities on SD-OCT.

Conclusion—SD-OCT can demonstrate photoreceptor abnormalities that correlate with the perifoveal ring seen with autofluorescence imaging of patients with CORD6. SD-OCT has significant potential for understanding and following the natural history of diseases such as CORD6.

Keywords

autofluorescence; cone-rod dystrophy; photoreceptor outer segments; spectral-domain OCT

Introduction

The cone-rod dystrophies are a group of degenerative diseases that are phenotypically and genetically heterogeneous. Cone-rod dystrophies manifest in childhood or early adulthood, and their common features include decreased visual acuity, abnormal color vision, and progressive visual field loss. Electroretinogram (ERG) testing demonstrates progressive loss of photoreceptor function. Cone function is lost first, but progressive disease ultimately leads to compromised rod function as well. Given that clinical exam findings are variable and can overlap with other diseases, the ERG is critical for the diagnosis.

Autosomal dominant, recessive, and X-linked inheritance patterns have been described for the cone-rod dystrophies. For the autosomal dominant cone-rod dystrophies, 9 genes and 2

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loci have been identified to date.¹ There is a paucity of literature describing histopathologic correlations with particular mutations of the cone-rod dystrophies. The advent of spectral domain OCT (SD-OCT) and autofluorescence imaging provides new opportunities to study genotype-phenotype correlations non-invasively in retinal degenerations of living patients.^{2,3} SD-OCT enables detailed evaluation of structural changes of the retinal layers, and autofluorescence imaging enables evaluation of lipofuscin accumulation within the retinal pigment epithelium (RPE). Autofluorescence imaging can detect changes that indicate photoreceptor dysfunction before the death of the photoreceptors.^{2,4} By studying a group of cone-rod dystrophy patients, Robson et al. have demonstrated that there is a perifoveal ring of increased autofluorescence associated with reduced rod and cone sensitivity. They suggest that the size of this hyperfluorescent ring correlates with age, is related to photoreceptor dysfunction but not death, and may stem from lipofuscin deposition secondary to outer segment shedding.² Lima et al. have used SD-OCT and autofluorescence to evaluate the ring of hyperfluorescence that can be found at the macula of patients with retinitis pigmentosa. They found that the hyperfluorescent ring marked a transition zone at which there is inner segment/outer segment (IS/OS) junction disorganization, a thinner outer nuclear layer, and a diminished external limiting membrane.⁴ We describe a patient diagnosed with cone-rod dystrophy 6 (CORD6) and discuss the implications of the SD-OCT and autofluorescence findings.

Case Report

A 13-year-old girl had progressive loss of vision in both eyes over the past 3 years. She had no prior medical or ophthalmic history. She denied any difficulty with color vision or night vision. There was no family history of genetic eye disease, and there was no history of consanguinity. The patient did not take any medications.

The corrected visual acuity for the right eye was 20/40 without pinhole improvement, and the left eye was 20/63 with pinhole improvement to 20/40. Slit lamp examination of the anterior segment was normal for both eyes. The intraocular pressures measured 17 mm Hg bilaterally. Dilated fundus examination was notable for a mild, granular appearance of the perifoveal RPE for each eye (Figure 1 A-D). The optic nerves were normal, and there was no vascular attenuation. There were no yellow flecks suggestive of Stargardt's disease. There were no pigment changes in the periphery.

A fluorescein angiogram showed a granular perifoveal appearance with hyperfluorescence from a few window defects (Figure 2). There was no dark choroid. Farnsworth D-15 testing showed normal hue discrimination in both eyes with a suggestion of errors along the tritan axis. Humphrey visual fields showed patchy loss of sensitivity within the central 10 degrees of each eye. An SD-OCT (Spectralis HRA-OCT, Heidelberg Engineering) demonstrated focal reflectivity abnormalities at the photoreceptor layer in each eye. These abnormalities start at the IS/OS junction and include the outer segment layer, suggesting lost or abnormal photoreceptor outer segments (Figure 4 A-B). The central subfield thickness, as measured by the SD-OCT, was 199 μ m for the right eye and 201 μ m for the left eye. The time-domain OCT (Stratus OCT, Carl Zeiss Meditec) recorded central subfield measurements of 134 μ m for the right eye and 143 μ m for the left eye, indicating an abnormally thin retina at the fovea of each eye. Autofluorescence (Spectralis HRA-OCT, Heidelberg Engineering, 488 nm) images revealed a mild, perifoveal ring of hyperfluorescence (Figure 4 A-B) in each eye. The abnormalities on SD-OCT began at the outer edge of the perifoveal ring seen on autofluorescence. Centrally, there was no hyperfluorescence, and this correlated with an area on the SD-OCT where there were more pronounced abnormalities and also thinning of the RPE (Figure 4 A-B). An ERG showed compromised cone-mediated inner retinal responses

with below normal amplitudes and normal latencies for both eyes (Table 1). The rod responses were normal for both eyes.

Genetic testing (Carver Lab, Iowa City, IA) revealed a heterozygous CGC>CAC nucleotide substitution at codon 838 of the *GUCY2D* gene. This results in an amino acid change of Arg838His and provides a molecular diagnosis of CORD6, an autosomal dominant cone-rod dystrophy.

Discussion

CORD6 (OMIM#601777) is caused by mutations in the retinal guanylate cyclase gene (*GUCY2D*) on chromosome 17p13.1. This gene encodes a membrane bound protein (RETGC-1) that helps synthesize cGMP from GTP in photoreceptor cells.⁵ This protein is critical to the regulation of photoreceptor activity by cGMP-gated cation channels. While RETGC-1 is present in all photoreceptors, it seems to have a higher concentration in cones than in rods.⁵ Codon 838 is part of a 3 codon sequence within the putative dimerization domain of the protein. The heterozygous Arg838His mutation has been previously reported for dominantly inherited CORD6.⁶ Interestingly, homozygous mutations in *GUCY2D* can lead to recessively inherited Leber's congenital amaurosis.⁷

Gregory-Evans et al. described the phenotype of a family with CORD6 associated with a heterozygous Glu837Asp/Arg838Ser mutation of *GUCY2D*.⁷ All affected individuals reported subnormal vision before 6 years of age, and many had pendular nystagmus. Peripheral field loss and nyctalopia did not occur until the fourth decade of life. Young patients had a "bull's-eye" maculopathy, and older patients developed peripheral bone-spicules. The only pediatric patient in their series was a 14 year-old. This was the only patient with testable color vision, revealing no color discrimination on a tritan axis. This 14 year old did have reduced cone and rod ERG responses. Our patient has a mild phenotype. Her vision abnormalities began by age 10, she did not have nystagmus, and her ERG showed reduced cone responses but normal rod responses. Indeed, Downes et al. have reported that patients with the Arg838His mutation display a milder phenotype than those with the Glu837Asp/Arg838Ser mutation.⁸ Early in the clinical course, it seems that the Arg838His mutation has a phenotype more similar to a cone dystrophy, but with aging, the rods will presumably become involved.

It has been suggested that RETGC-1 plays a role in synaptic transmission in addition to its role in phototransduction in the photoreceptor outer segment.⁷ Early in the disease, the key defect may be at the photoreceptor synaptic endings as opposed to the outer segments. Supporting this possibility are histologic findings from a cone-rod dystrophy patient demonstrating abnormalities of photoreceptor synaptic endings with relative preservation of the outer segments.⁹ This patient was a 43 year-old; there was no reported mutation associated with the histopathology.

To our knowledge, there are no reports of histopathology in mutationally confirmed CORD6. The striking feature of the CORD6 patient reported here is the appearance of the IS/OS junction and the outer segment layer seen on SD-OCT. It is generally accepted that the IS/OS junction normally appears on SD-OCT as a uniformly hyperreflective band above the retinal pigment epithelium. Although complete consensus on the exact location of outer segments is lacking, it follows that the photoreceptor outer segments are located between the IS/OS junction and the RPE complex. In this patient, the focal areas of irregularities start at the IS/OS junction and extend towards the RPE complex. These structural abnormalities suggest abnormal, and perhaps absent, outer segments. This is consistent with a histopathologic report of a 75 year-old patient with autosomal dominant cone dystrophy of

unknown genetic type who showed extensive loss of photoreceptors at the fovea.¹⁰ Abnormalities at the IS/OS junction have been seen in other patients with retinal degenerations.^{3, 4} Presumably, there are individual or patchy abnormalities of photoreceptors at initial stages of at least some cone dystrophies, which progress to widespread dysfunction and loss with aging.

The autofluorescence images showed a perifoveal ring of hyperfluorescence that has been described in other patients with mutations of *GUCY2D*.⁸ This ring roughly corresponds to the area of perifoveal RPE changes seen on the fundus photos. In patients with retinitis pigmentosa, Lima et al. demonstrated that structural changes at the IS/OS junction of SD-OCT images correlated with the perifoveal ring seen on autofluorescence imaging.⁴ Similarly, we found that the SD-OCT abnormalities correlate with the outer edge of the hyperfluorescent ring seen on autofluorescence imaging. Presumably, the photoreceptor abnormalities lead to increased lipofuscin within the RPE. It is logical to conclude that there is a structure – function relationship such that the SD-OCT and corresponding autofluorescence abnormalities represent areas of photoreceptor dysfunction. Indeed, Robson et al. found that the autofluorescent perifoveal ring corresponded to areas of photoreceptor dysfunction in patients with cone-rod dystrophy.² Nevertheless, the structural changes of the photoreceptors are most pronounced at the center of the fovea in our patient, and there is no hyperfluorescence corresponding to this area on the autofluorescence imaging. The fovea normally has a reduced autofluorescence signal because of the absorption by luteal pigment. In addition to this absorption by the luteal pigment, the lack of central hyperfluorescence in our patient may also be related to the thinning of the RPE layer found only at the center of the fovea. This central area may be at a more advanced stage of degeneration than the area that corresponds to the ring of hyperfluorescence, and the central thinning of the RPE is likely an area of incipient atrophy. One would expect that eventually there might be complete loss of the photoreceptors at the fovea and more extensive atrophy of the RPE, leading to an increased area of hypofluorescence on autofluorescence imaging and further changes on SD-OCT. Although only histopathology can provide absolute proof, our SD-OCT findings strongly suggest that, early in the disease, it is the loss or disease of photoreceptor outer segments that leads to decreased vision rather than a generalized synaptic dysfunction as previously suggested.^{7, 9} The abnormal photoreceptors most likely are cones, given that the abnormalities are seen predominantly at the center of the fovea. The interpretation that these reflectivity abnormalities represent cone dysfunction is further supported by the decreased cone amplitudes seen on the ERG. The SD-OCT suggests that there is early individual loss or disease of photoreceptor outer segments, as opposed to only synaptic transmission dysfunction, in this 13 year-old patient with mild loss of visual acuity (at the 20/40 level) and mild color vision abnormalities. Given that all of the cones have this mutation, it is interesting to consider why certain cones have abnormal reflectivity at a young age while those of neighboring cones in the fovea do not.

While an ERG is still essential for making a diagnosis of a cone-rod dystrophy, SD-OCT contributes to the diagnosis and allows visualization of the photoreceptor abnormalities. Histopathologic studies of cone-rod dystrophies, especially at early stages of the diseases, are limited by the availability of well-preserved donor eyes. The “in vivo histology” that can be provided by SD-OCT has significant potential for understanding and following the natural history of such diseases. Furthermore, as clinical trials for photoreceptor rescue by gene therapy advance, SD-OCT and autofluorescence imaging will be useful to monitor treatment responses.

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Figure 1. Fundus photographs of the right (A) and left (C) eye showing a mild, granular appearance of the perifoveal RPE and normal light reflex at the fovea. Enlarged views of the fovea of the right (B) and left (D) eyes are shown.

Figure 2. Fluorescein angiography of the right eye at 22 seconds shows the mild, granular appearance of the perifoveal RPE with hyperfluorescence from a few window defects.

Figure 3.

Autofluorescence and corresponding spectral domain OCT images through the fovea of the right eye of a normal 14 year old girl. High magnification images of the OCT are shown with labels for each layer. NFL, nerve fiber layer; GCL, ganglion cell layer; IPL, inner plexiform layer; INL, inner nuclear layer; OPL, outer plexiform layer; ONL, outer nuclear layer; ELM, external limiting membrane; IS/OS, inner segment and outer segment junction; OS, outer segments; RPE complex, retinal pigment epithelium complex. Note the smooth, uniform quality of the IS/OS, OS, and RPE complex layers. The RPE complex layer is of equal thickness throughout the OCT image.

Figure 4.

Autofluorescence and corresponding spectral domain OCT images through the fovea of the right (A) and left (B) eye of this patient with cone-rod dystrophy 6. The autofluorescence image of each eye shows a mild perifoveal ring of hyperfluorescence demarcated by the vertical lines. The SD-OCT image of each eye shows irregularities at the layers representing the junction of the inner segments and outer segments (IS/OS) as well as the photoreceptor outer segments. The vertical lines on the SD-OCT image correspond to the vertical lines on the autofluorescence image. The outer pair of vertical lines on the SD-OCT image also marks the boundaries of the SD-OCT abnormalities, thus demonstrating a correlation between the SD-OCT abnormalities and the area of the hyperfluorescent ring seen on autofluorescence imaging. High magnification images of each SD-OCT are shown for each eye. These images show abnormalities (black arrow) of the IS/OS junction and the

photoreceptor outer segments, suggestive of loss of the structural integrity of the photoreceptors. The lower right inset image for each eye demonstrates that the layer corresponding to the retinal pigment epithelium complex is thinner at the fovea, as measured with calipers (double headed arrows).

Table 1**ERG Findings**

	OD	OS
Cone amplitudes (72–305 [μV]mV)	56	48
Cone implicit times (26–32 ms)	29	28
Rod amplitudes (84–312 [μV]mV)	346	276
Rod implicit times (62–83 ms)	88	81

An ERG was performed in accordance with the International ISCEV Standards. A cone ERG was recorded under photopic/light-adapted conditions with a 0-dB flash. A rod ERG was recorded under scotopic/dark-adapted conditions with a 24-dB flash. The normal ranges are listed in the left column.

OD, right eye; OS, left eye.