A Young Boy with Blurry Vision

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Introduction:

A 9-year-old Caucasian male was referred to our office for evaluation of a potential macular dystrophy. The patient reported occasional blurred vision in both eyes for the past two to three months. He had no prior history of any ocular disorders and his medical history was unremarkable. His mother reported that the patient was born full-term and had an uneventful birth history. He was healthy and had met developmental milestones appropriately. The only medication he took was a daily multivitamin. Other than occasional blurred vision his review of systems was negative. Further, he denied any prior trauma to either eye. Patient did endorse brief periods of gazing at the sun, but not for prolonged periods of time and denied playing with any laser pointers. His family history was negative for any ocular problems or significant medical disorders. The patient denied any issues with nyctalopia.

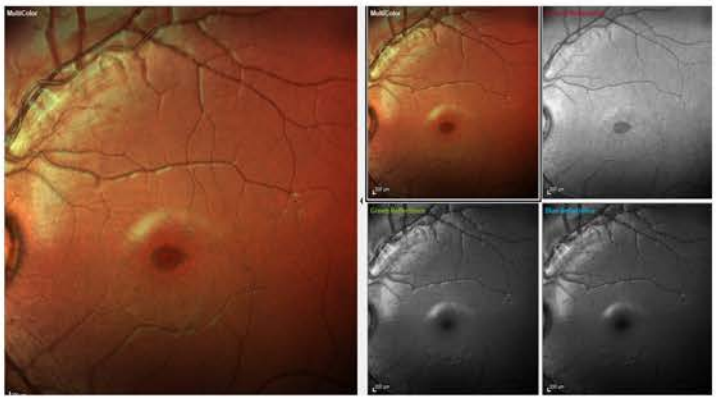

Figure 1 (top): A multicolor image of the right eye demonstrating central pigmentation and atrophy.

Figure 2 (bottom): A multicolor image of the left eye demonstrating central pigmentation and atrophy.

Exam:

Visual acuity testing without correction was 20/60 in each eye. Pinhole occluder testing yielded no improvement. Intraocular pressures were within normal limits. Confrontational visual field testing and ocular motility were both full. There was no evidence of an afferent pupillary defect in either eye. His anterior segment exam was unremarkable. Dilated fundus examination demonstrated central macular pigmentation with focal atrophy at the fovea. His retinal vascular and periphery appeared normal (Figures 1 and 2).

OCT revealed focal outer retinal disruption in the subfoveal area (Figure 3). OCT-Angiogram did not demonstrate any evidence of macular leakage of abnormal vessel growth (Figures 4 and 5). Fundus autofluorescence (FAF) demonstrated focal granularity in the central macula (Figure 6).

The differential for his presentation included solar retinopathy, cone-rod dystrophy, rod-cone dystrophy, and KCNV2 retinopathy.

Work-up:

Given the differential diagnosis, a multifocal electroretinogram (mfERG) and genetic testing were obtained. mfERG did not demonstrate findings consistent with cone dystrophy, but did show atypical waveforms. Genetic testing identified two pathogenic variants in ABCA4 gene.

Typically, ABCA4 mutations are associated with Stargardt's disease, which this patient did not appear to have. Based on examination, multimodal imaging, and genetic testing our patient is suspected to have KCNV2 retinopathy or a variation of it. He has thus far demonstrated stability in both visual acuity and examination and is being followed annually. Documentation has

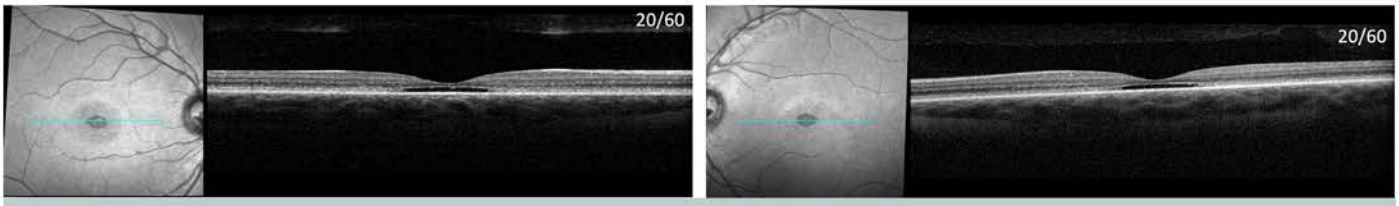

Figure 3: OCTS of the right and left eye with focal outer retinal disruption.

been provided to the patient to ensure he has proper adjustments made in school to compensate for his visual impairment as well as visual aids.

Discussion:

KCVN2 Retinopathy (OMIM #610356) or KCNV2-associated retinopathy is an autosomal recessive cone-rod dystrophy located on chromosome 9p24. It was first described in by Gouras et al in 1983 in patients with a cone dystrophy and nyctalopia. Fundoscopic examination will reveal loss of the foveal light reflex and an increased granularity to the macula. ERG testing in these patients tends to have a characteristic pattern of cone dysfunction with a supernormal rod response. This affords another name for this disease process, "Cone Dystrophy with Supernormal Rod Response (CDSRR)." CDSRR was linked to the KCNV2 by Wu et al in 2006. The gene encodes for a voltage-gated potassium channel that is responsible for setting the resting potential of photoreceptors as well as their voltages responses. When mutations are present in this gene it leads to cellular instability and dysfunctional photoreceptors. In the United States it has an incidence of 5 new cases per year with an estimated frequency of 1/865,000 persons. Patients most often present in the first or second decade of life with poor vision, red-green axis dyschromatopsia, photophobia, and a central scotoma. The disease can occur in younger children and when it does they may display an abnormal head posture, nystagmus, or head shaking. These findings in younger children are non-specific and must be differentiated for other causes of poor vision and abnormal head posturing in infancy. Patients may also note nyctalopia, although this is variable as the peripheral retina does not appear to demonstrate abnormality. In fact, on examination the pathology will be most notably seen in the central macula with a normal appearing retinal periphery. The patient's refraction may show a mild or moderate myopia but the disease is not always associated with myopia. Multimodal imaging is helpful in guiding diagnosis. OCT will show discontinuities, attenuation, or loss in the subfoveal ellipsoid zone (EZ). In later stages more extensive loss and atrophy of the EZ and retinal pigment epithelium (RPE) are seen (Figure 7). FAF may show increased foveal signal, an appearance similar to a bull's eye maculopathy, and a perifoveal fing with hyperautofluorescence as well as central atrophy. Foveal granularity may also be observed. Younger patients will tend to demonstrate a perifoveal ring of increased autofluorescence that will later evolve into an area of hypoautoflouresence indicating RPE and photoreceptor loss. Aside from symptom management, such as tinted glasses for photophobia, and access to low vision aids there is no treatment or cure for KCNV2 retinopathy. Gene therapy is an active area of research and KCNV2 retinopathy may prove to be a suitable target for gene therapy

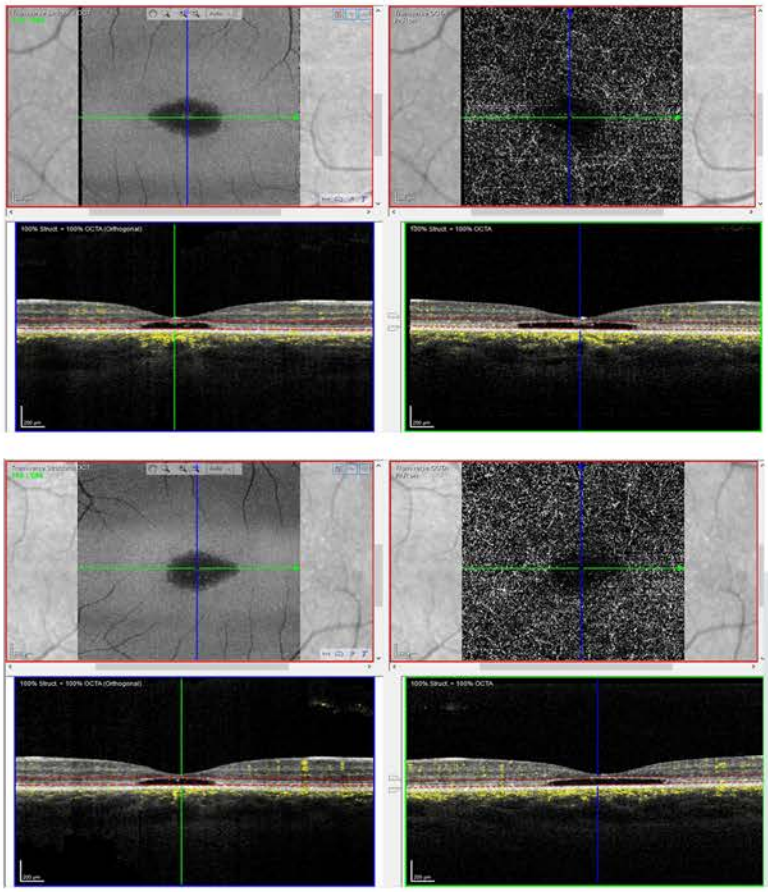

Figure 4 (top): An OCT- angiogram of the right eye without evidence of macular leakage.

Figure 5 (bottom): An OCT-angiogram of the right eye without evidence of macular leakage.

given that the KCNV2 is a small gene and may be able to be packed into a viral vector. Additionally, there are rodent models that mimic human disease and can be targeted for trials of therapeutic intervention.

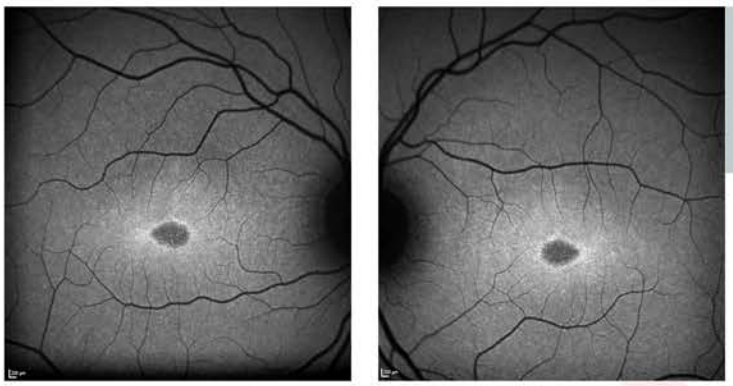

Figure 6: Fundus autofluorescence images of the right and left eyes demonstrating focal granularity of the central macula.

Although our patient did not have a direct pathogenic variant in the KCNV2 gene, ABCA4 mutations have multiple phenotypic presentations and KCNV2 has some overlap with a pattern that ABCA4 mutations demonstrate. The overlap between these two cases is the bull's eye maculopathy-like appearance with central atrophy. Of course our knowledge will continue to expand as the genetic database continues to evolve and grow and more phenotypic variations are identified.

Take Home Points:

- KCNV2 retinopathy is a cone dystrophy with a supernormal rod response.
- KCNV2 retinopathy is autosomal recessive.
- Genetic testing can be a valuable tool to help elucidate potential causes of retinal changes.
- When considering a genetic disorder or inherited retinal dystrophy, obtaining family history is important as it can help guide the differential diagnosis.

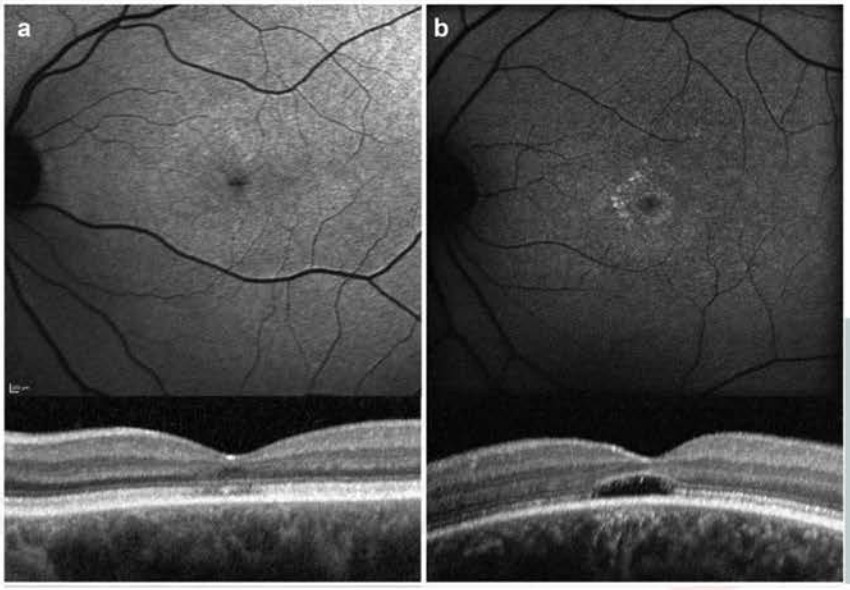

Figure 7: An OCT from the article by Guimaaraes et al showing the subfoveal EZ changes that can be seen with KCNV2 retinopathy.

References:

1. Georgiou M, Robson AG, Fujinami K, et al. KCNV2-Associated Retinopathy: Genetics, Electrophysiology, and Clinical Course—KCNV2 Study Group Report 1. *Am J Ophthalmol*. 2021;225:95-107. doi:10.1016/j.ajo.2020.11.022

2. Gouras P. Cone Dystrophy, Nyctalopia, and Supernormal Rod Responses: A New Retinal Degeneration. *Arch Ophthalmol*. 1983;101(5):718. doi:10.1001/archopht.1983.01040010718003

3. Guimaraes TACD, Georgiou M, Robson AG, Michaelides M. *KCNV2* retinopathy: clinical features, molecular genetics and directions for future therapy. *Ophthalmic Genet*. 2020;41(3):208-215. doi:10.1080/13816810.2020.1766087

4. Wu H, Cowing JA, Michaelides M, et al. Mutations in the Gene KCNV2 Encoding a Voltage-Gated Potassium Channel Subunit Cause "Cone Dystrophy with Supernormal Rod Electroretinogram" in Humans. *Am J Hum Genet*. 2006;79(3):574-579. doi:10.1086/507568

5. Gill JS, Georgiou M, Kalitzeos A, Moore AT, Michaelides M. Progressive cone and cone-rod dystrophies: clinical features, molecular genetics and prospects for therapy. *Br J Ophthalmol*. 2019;103(5):711-720. doi:10.1136/bjophthalmol-2018-313278

6. Cremers FPM, Lee W, Collin RWJ, Allikmets R. Clinical spectrum, genetic complexity and therapeutic approaches for retinal disease caused by ABCA4 mutations. *Prog Retin Eye Res*. 2020;79:100861. doi:10.1016/j.preteyeres.2020.100861

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