THE **RETINA** PARTNERS

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Case of the Month – November 2021

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A 48-year-old male was referred for a second opinion regarding vision loss in both eyes. The patient conveyed that his vision loss in the left eye began approximately 15 years ago, starting as multiple, stationary, focal, gray dots in the vision of his left eye, and then slowly growing and coalescing over time, causing him to lose his central vision. He presents with complaints of multiple, stationary, focal, gray dots in his right eye over the past 5 years. The patient stated he was given a diagnosis of dry macular degeneration by a retina specialist elsewhere and told to take AREDS2 vitamins, which he has been taking for the past 5 years. He was referred by his ophthalmologist for a second opinion.

Visual acuity was 20/25 in the right eye (OD) and 20/350 in the left eye (OS). Intraocular pressures were 18 OD and 19 OS. Pupils were equal, round, reactive, and there was no relative afferent pupillary defect. Slit lamp exam was unremarkable aside from 1+ nuclear sclerosis and trace cortical cataract in both eyes. Dilated fundus examination revealed vitreous syneresis in both eyes and multiple drusenoid and fleck-like yellow deposits in the macula of the right eye, with no peripheral bone spicules or other chorioretinal findings. There was large, central geographic atrophy and a few drusenoid and fleck-like yellow deposits noted in the macula of the left eye, with no peripheral pathology.

On autofluorescence imaging, there were multiple hypoautofluorescent foci in the right eye, corresponding to the fleck-like deposits. In the left eye, there was large central hypoautofluorescence

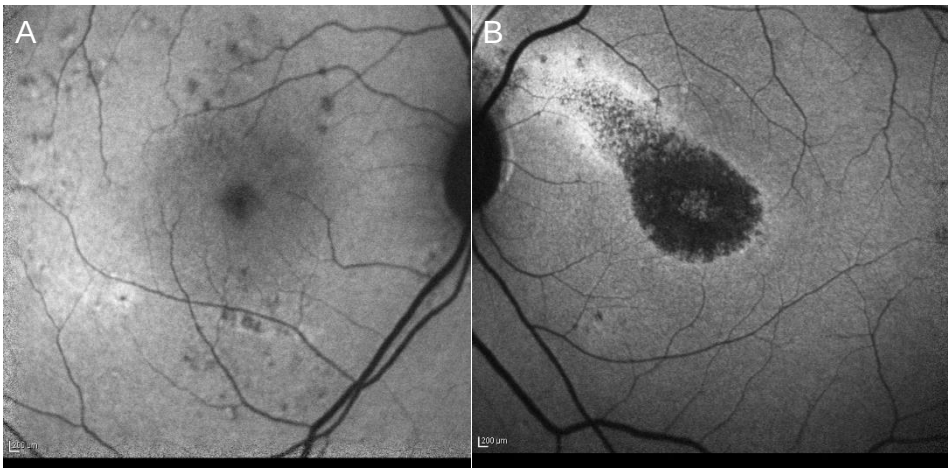


Figure 1: Fundus autofluorescence of the (A) right eye showing multiple hypoautofluorescent foci and of the (B) left eye showing large, central hypoautofluorescence with surrounding hyperautofluorescence, most prominent superonasally.

corresponding to the geographic atrophy with a small rim of surrounding hyperautofluorescence and larger patch of hyperautofluorescence in the superonasal macula (Figure 1). On optical coherence tomography, there were multiple drusenoid deposits in the right eye without atrophy (Figure 2); in the

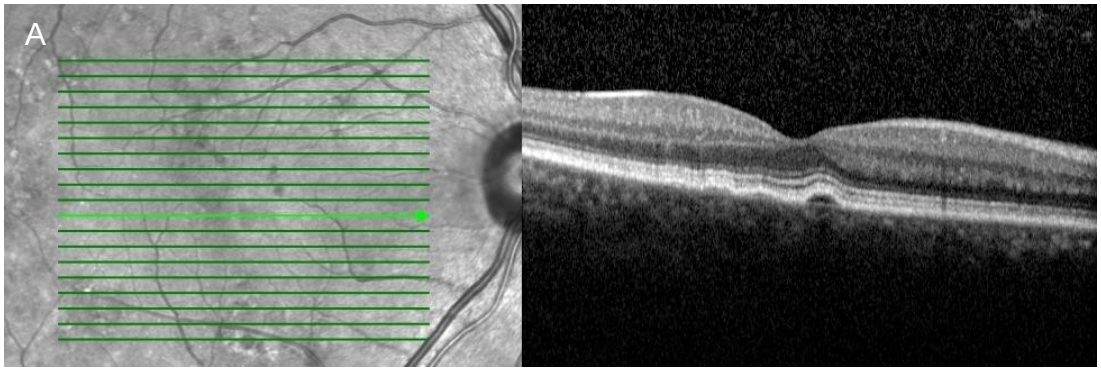
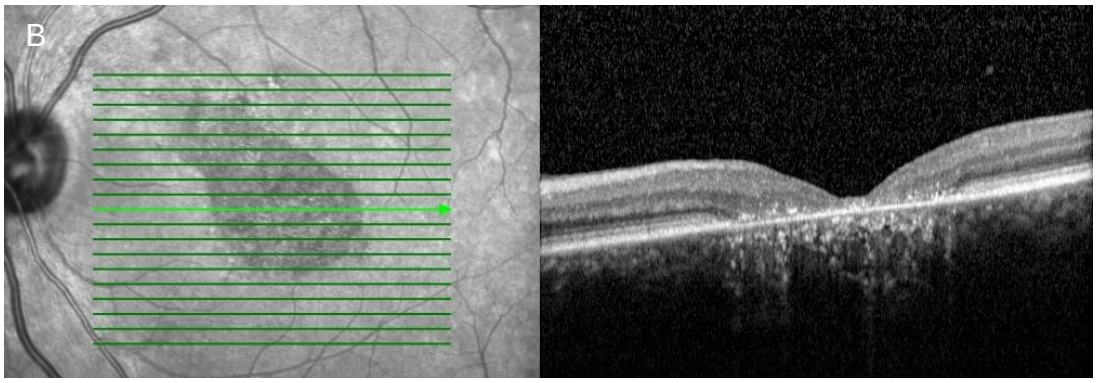


Figure 2: Optical coherence tomography of the (A) right eye showing multiple drusenoid deposits and of the (B) left eyes showing large, central geographic atrophy with multiple, hyperreflective, outer-retinal foci.



left eye there was large, central geographic atrophy, with loss of the ellipsoid zone band and retinal pigment epithelium, as well as many hyperreflective foci in the outer retina. Fluorescein angiography of the right eye revealed hyperfluorescent staining of the deposits and hyperfluorescence consistent with a window defect in the left eye due to geographic atrophy, with staining of deposits (Figure 3).

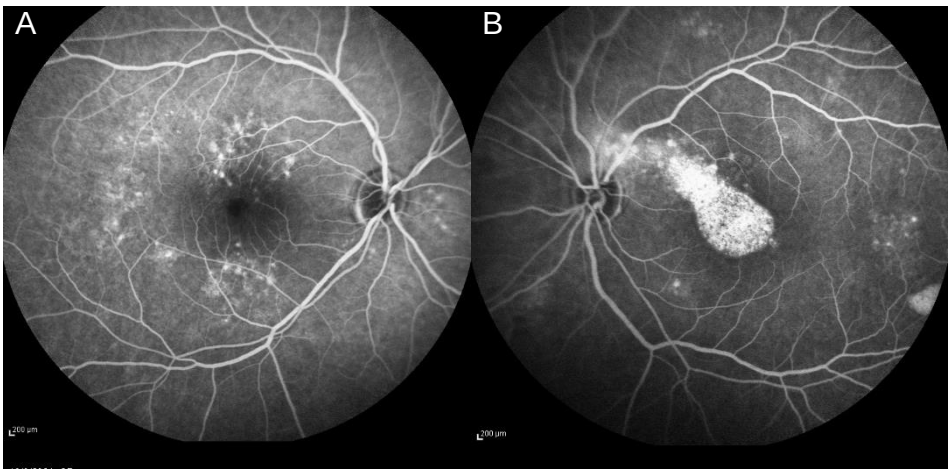


Figure 3: Fluorescein angiography of the (A) right eye showing hyperfluorescent staining of the drusenoid deposits and of the (B) left eye showing large, central hyperfluorescence corresponding to the geographic atrophy, as well as several foci of staining corresponding to the deposits.

Clinical Course:

The patient was advised that given his age, history, and clinical presentation, there was heightened concern for an inherited retinal dystrophy, rather than macular degeneration. The patient gave informed consent for a buccal swab to be performed and sent for genetic testing, a service we are able to provide free of cost to our patients in collaboration with our industry partners. The sample was found to have one pathogenic mutation, as well as a second variant of uncertain significance in the BBS10 gene. This result is consistent with autosomal recessive Bardet-Biedl syndrome (however, our patient has no family history of similar visual problems or of Bardet-Biedl syndrome). The results and their significance were discussed with the patient. The guarded prognosis and possibility of progression in his better-seeing right eye were discussed. The lack of currently available treatments for his disease was discussed, as well as the opportunity for ongoing or future clinical trial participation. Finally, we discussed the current status of translational science by way of gene therapy and potential future therapies. The patient was given follow-up and an appointment with a genetic counselor.

Discussion:

Bardet-Biedl Syndrome (BBS) is an inherited retinal dystrophy with systemic congenital abnormalities; it has a phenotypic expression along the retinitis pigmentosa (RP) spectrum, though patients with BBS do not typically have peripheral bone spicules (as typically seen in RP). It is most commonly inherited in an autosomal recessive manner with mutations in any one of at least 15 known BBS genes, though some cases of BBS require a third mutation in a second BBS gene in order for the disease to express itself (called trigenic inheritance).

In 1920, Bardet described a patient with retinopathy, polydactyly, and obesity. In 1922, Biedl described a patient with the fourth and fifth cardinal features: mental retardation and hypogenitalism. The prevalence of BBS has been described as 1 in 160,000 in Switzerland and as 1 in 13,500 in Kuwait.

There can be overlap in the clinical findings of patients with age-related macular degeneration (AMD) and macular dystrophies (including BBS). Patients with atypical features, who are younger than the expected age for AMD may benefit from further evaluation and genetic testing. Genetic testing for macular dystrophies has become widely available and free of cost to the patient, in most cases.

BBS differs from typical retinitis pigmentosa in that the visual acuity fails early in the disease course and usually the fundus shows little pigmentary dispersion until later stages. Macular lesions and atrophy of the RPE or choriocapillaris often develop early and prominently as the disease progresses. The macular findings may include macular wrinkling, preretinal membrane formation, and leakage on fluorescein angiography from paramacular capillaries. The electroretinogram may show a rod-cone loss, and in other cases a cone-rod loss. The absence of pigmentary deposits in BBS has also led some to refer to it as retinitis pigmentosa sine pigmento. The onset of night blindness is recognized by a mean age of 8.5 years and legal blindness by a mean age of 15.5 years of age. Approximately 73% of patients reach legal blindness by age 20 and 86% by the age of 30 years.

The 5 cardinal features of BBS include rod/cone dystrophy, obesity, polydactyly (multiple fingers), intellectual disability, and hypogonadism/infertility. Many patients with BBS also have renal dysfunction. Incomplete manifestation of the five cardinal features is the rule rather than the exception in BBS, with one study showing 45% of cases were incomplete and another showing 76.5% were incomplete. Some have argued that at least 4 of the 5 features should be present to establish the diagnosis conclusively and that retinopathy must be one of the features, but this was prior to widespread and affordable availability of genetic testing.

In the case of our patient, he presented with only the ocular findings of the disease, with progressive photoreceptor (cone-loss predominantly) and outer retinal loss in both eyes, with advanced geographic atrophy in the macula of the left eye, but he did not have other systemic features of the disease, such as obesity, polydactyly, or intellectual disability. Thus, our patient suffers from Bardet-Biedl-like disease, but not the complete syndrome. We anticipate that as genetic testing has become more widespread and affordable for patients, there will be a growing number of patients identified who suffer from only partial phenotypic expression of this disease (probably rod/cone dystrophy), without having all of the cardinal systemic features. There are multiple completed and ongoing global clinical trials for patients with BBS, which to date have mostly focused on mapping out genotypic/phenotypic expression. There is hope that gene therapy may one day be on the horizon for patients with BBS, as we have seen for patients with Leber Congenital Amaurosis.

Take Home Points: Bardet-Biedl Syndrome (BBS)

- The 5 cardinal features of BBS are rod/cone dystrophy, obesity, polydactyly, intellectual disability, and hypogonadism/infertility. Many patients also have renal dysfunction.
- Consider the possibility of an inherited retinal dystrophy when examining a younger patient with clinical findings suggestive of macular degeneration.
- We are able to offer comprehensive, free genetic testing to patients with suspected inherited retinal dystrophies. Genetic mapping may position the patient to secure enrollment into future clinical trials for the treatment of their disease.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