Article • Observing Beyond the Eyes: A Rare Case Report of Pigmentary Retinopathy

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ABSTRACT

Background: This case highlights how a patient's physical extra-ocular features and behavioral characteristics guided an eye exam, where the finding of atypical retinitis pigmentosa (RP) led to the final diagnosis of Bardet-Biedl Syndrome (BBS). BBS is a serious multisystem condition consisting of atypical RP, polydactyly, central obesity, developmental delays, hypogonadism, and renal dysfunction.

Case Report: A thirteen-year-old Hispanic female was seen at the University Eye Center due to longstanding decreased vision, which had not improved with the use of spectacles. The patient had a history of developmental delays, central obesity, and nyctalopia. Upon observation, a history of polydactyly was noted, leading to the suspicion of BBS and possible correlated retinal changes. This finding prompted further investigation, and the patient was diagnosed with atypical RP associated with BBS. Further management involved referrals for low vision and social services.

Conclusion: The diagnosis and management for this patient relied heavily on close observation of her physical features. BBS is not always diagnosed at birth, unless polydactyly is present. Otherwise, the condition may be diagnosed when systemic manifestations have become more advanced. A more timely diagnosis allows proper treatment and management to prevent life-threatening consequences. This case serves to remind eye care practitioners to assess patients as a whole and not to focus only on the eyes.

Keywords: Bardet-Biedl syndrome, pigmentary retinopathy, retinitis pigmentosa, polydactyly, retina

Introduction

The list of diseases and syndromes with associated ocular manifestations is extensive. Some syndromes, such as Down syndrome, have easily distinguishable physical characteristics, but some, such as Sjögren syndrome, may display more subtle characteristics. Some conditions are diagnosed at birth or later in life, and others may go undiagnosed, such as Kleinfelter syndrome.[1] Some disorders are first discovered through ocular examinations, which was the instance for the following case of suspected Bardet-Biedl syndrome (BBS). Knowledge of specific conditions and their associated ocular complications can help guide an eye examination with additional ancillary testing and appropriate treatment and management for the patient.

BBS is a rare genetic disorder with an autosomal recessive hereditary pattern. The prevalence is 1 in 100,000 people in North America and Europe but is significantly greater in isolated communities such as Kuwait and Newfoundland, where the prevalence increases to 1 in 13,500 people.

BBS is also sometimes referred to as Laurence-Moon-Bardet-Biedl syndrome (LMBBS). Laurence and Moon first coined Laurence-Moon syndrome (LMS) in 1866 for a condition involving retinitis pigementosa (RP), short stature, hypogonadism, mental deficiency, and spastic paraparesis.[2,3] In the 1920s, Bardet and Biedl noted patients with similar manifestations of LMS but who also had polydactyly, and they developed the diagnosis of BBS.[2] Mutations in BBS genes have been found in both LMS and BBS, so both terms have been used interchangeably, although BBS is now the generally used term. There are twenty-one identified BBS genes to date.[4] The disease is caused by dysfunction of the primary cilium, a cellular organelle.[5]

Cilia are necessary for cell signaling to maintain proper development and homeostasis in a broad range of tissues in the body, including the retina, kidneys, and central nervous system.[5,6] In the retina, the affected cilia are those that link the photoreceptor inner and outer segments, resulting in retinal degeneration.[5]

The following case describes how an extensive case history and observations beyond the eyes can help steer the exam. The history of developmental delays and the presence of distinct physical features such as polydactyly and central obesity led to the finding of atypical RP and ultimately, to the likely diagnosis of BBS.

Case Report

Initial Visit

A thirteen-year-old Hispanic female presented to the University Eye Center (UEC) for a vision evaluation. Her school referred her as they were concerned that she could not see well. The patient seemed to be cognitively delayed and minimally verbal. Her aunt and grandmother, who voiced similar complaints, accompanied the patient as the mother was deceased. The patient had a spectacle prescription from a prior exam eight months ago, but she reported that she was still unable to see well through the current correction. The patient's aunt also noted that the patient's vision had seemed to become especially poor in dark environments. Consequently, the patient needed to feel around the walls to ambulate.

Ocular history was remarkable for spectacle correction since age five, but the patient's aunt reported that her glasses had never seemed to be able to correct the patient's vision fully. The patient's aunt and grandmother could not recall any other remarkable findings from previous eye examinations.

Birth history was remarkable for premature birth at seven months' gestation, with a low birth weight of one pound and three ounces. The patient remained in the hospital for two months and received oxygen therapy. The patient's aunt reported that the birth mother consumed alcohol, smoked, and used drugs during the pregnancy. The patient was developmentally delayed and was in a special education classroom.

No systemic conditions were reported. The patient was not taking any medications and had no known allergies. The patient's family history was unremarkable.

The current glasses prescription was +1.50-0.50x150 in the right eye and +2.25-2.25x020 in the left eye. Refraction revealed no change to the glasses prescription. Visual acuity was measured with Snellen single letters with crowding bars. The best-corrected visual acuity (BCVA) was 20/150 in the right eye, 20/200 in the left eye, and 20/80 with both eyes. The refractive error was mildly amblyogenic in the left eye due to greater meridional anisometropia in that eye. However, the refractive error was inconsistent with the amount of reduced visual acuity found in the right and left eyes.

Pupils were equal, round, and reactive to light, with no afferent pupillary defect. Confrontation visual fields were full to kinetic red binocularly. Extraocular motilities were full but qualitatively poor. Alignment testing revealed a small-angle intermittent left exotropia at near with poor motor control. Stereopsis was present but reduced. Color vision was unable to be tested due to poor cooperation.

Anterior segment evaluation revealed anterior blepharitis of both eyelids and an internal hordeolum of the right upper lid. Intraocular pressures were normotensive and equal in both eyes with the iCare tonometer. Dilated fundus exam revealed mild diffuse optic nerve head pallor of the right and left eyes. The retina was flat, and blood vessels were clear in the left and right eyes to the extent seen due to fleeting views from poor patient cooperation.

Upon observation, there was a small raised nodule on the side of the patient's left hand. When questioned about the lesion, the patient's aunt and grandmother reported that the patient was born with an extra finger on the left hand and an extra toe on each foot. The extra digits were surgically removed when the patient was younger at an unknown age. The patient also displayed mild abdominal obesity.

With the combined knowledge of the patient's characteristics of developmental delay, history of polydactyly and central obesity, and symptoms of decreased night vision, retinal changes associated with BBS were suspected. As a result, fundus photos with fundus autofluorescence images using the Optos Daytona were taken to determine any presence of retinopathy.

The fundus photos of the right and left eyes (Figures 1a and 1b, respectively) revealed depigmented areas greater in the right eye than the left eye in the posterior pole along the temporal and nasal arcades and perifoveally. There was a small clump of pigment along the inferotemporal arcade in the right eye. Retinal thinning was present nasal to the optic nerve in both eyes. A foveal reflex was present in both eyes. The arteries were attenuated in both eyes. The optic nerve had mild diffuse pallor in both eyes with moderate cup-to-disc ratios.

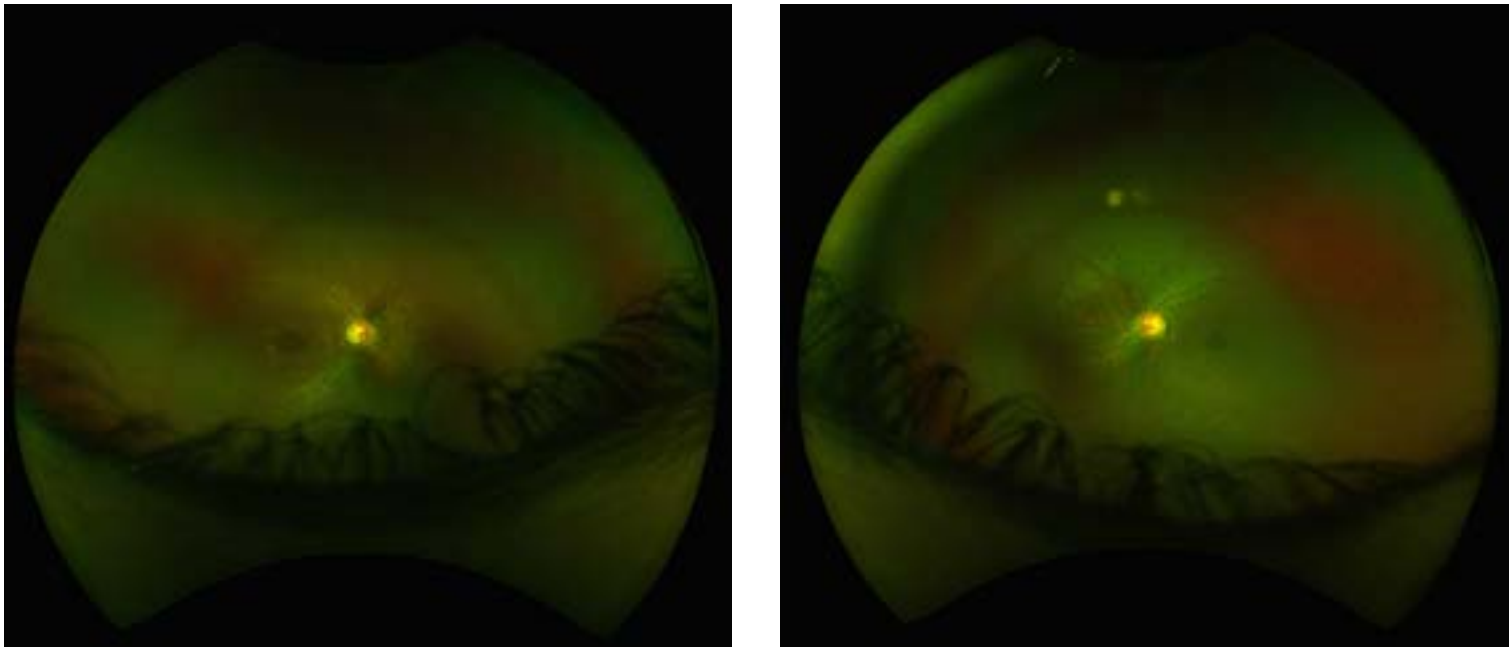


Figure 1. a) *Optos fundus photo of the right eye displaying depigmentary changes, attenuated arteries, and mild optic nerve head pallor*
b) *Optos fundus photo of the left eye displaying depigmentary changes, attenuated arteries, and mild optic nerve head pallor*

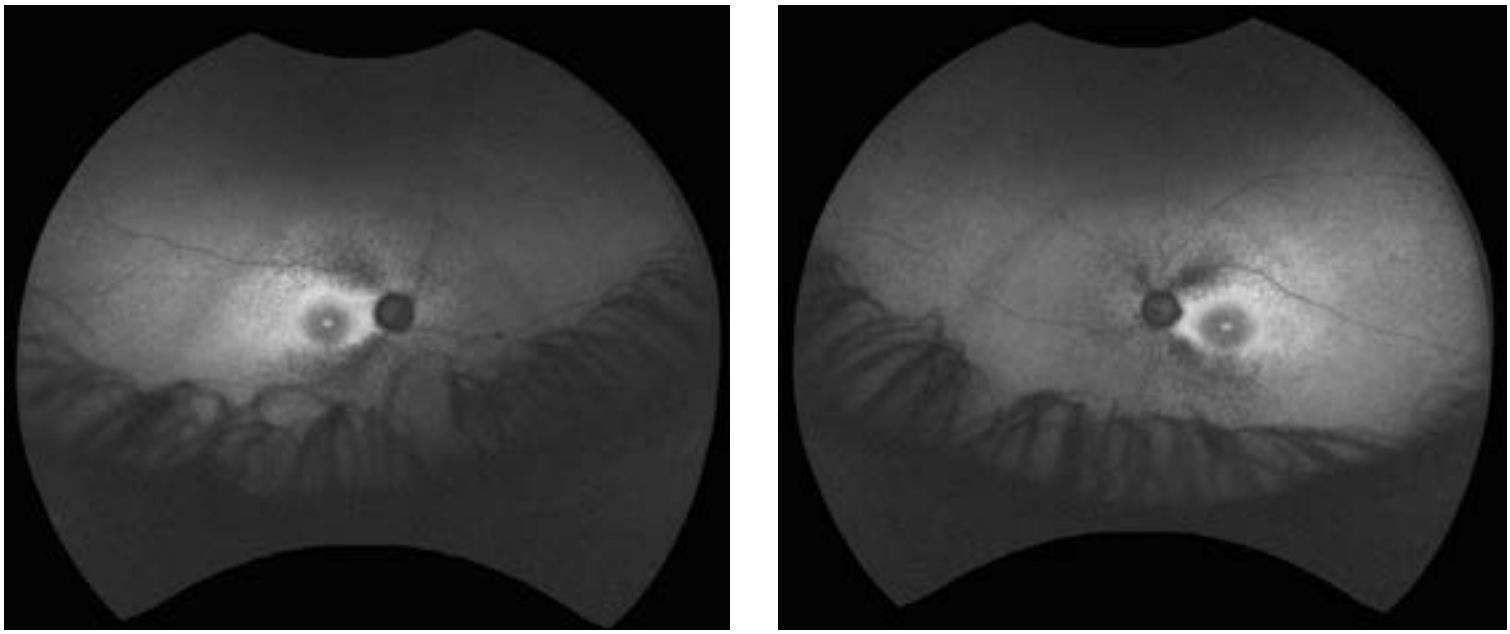


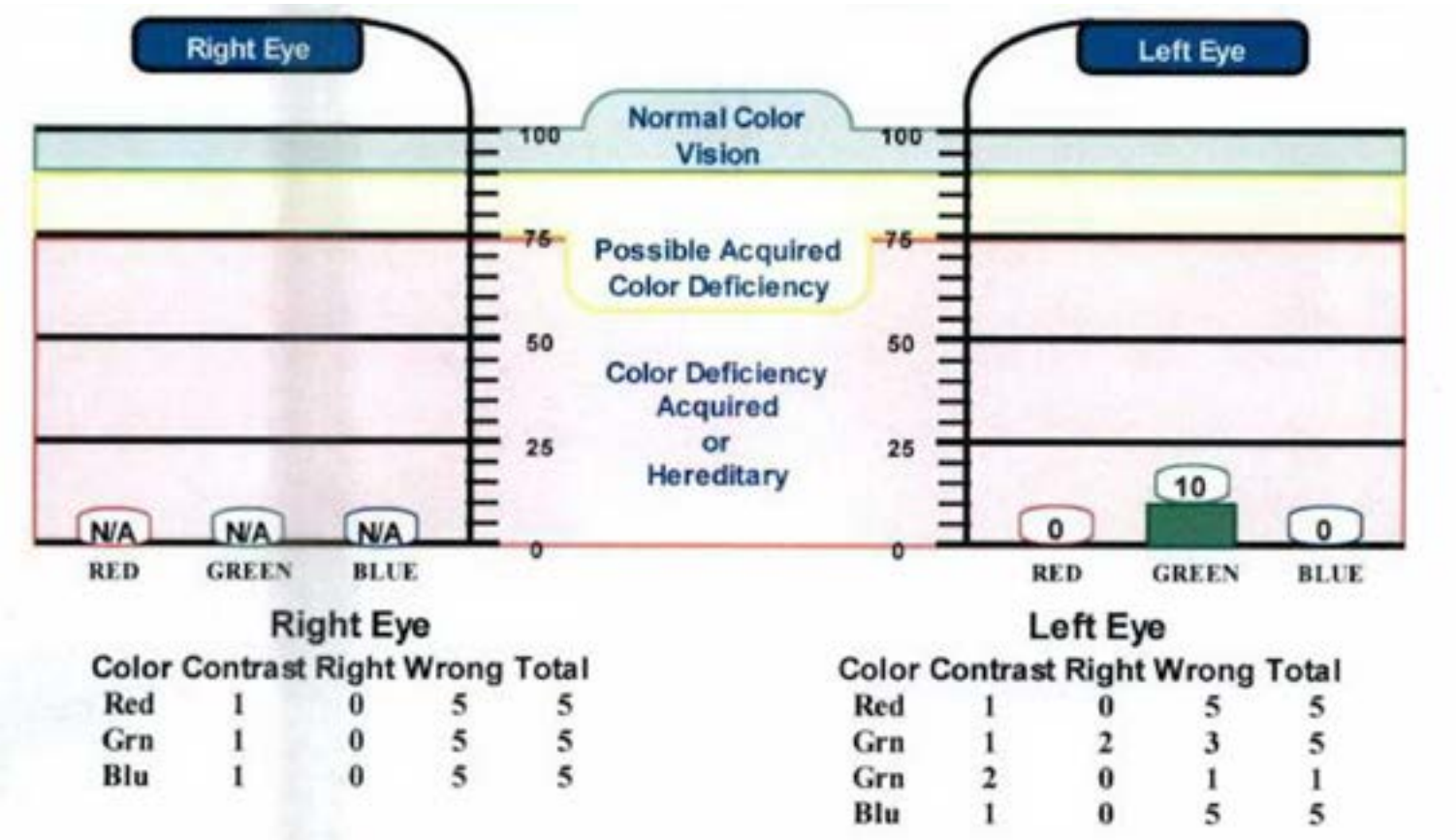
Figure 2. a) *Fundus autofluorescence of the right eye displaying alternating rings of hypo- and hyper-autofluorescence*
b) *Fundus autofluorescence of the left eye displaying alternating rings of hypo- and hyper-autofluorescence*

Fundus autofluorescence revealed alternating rings of hypofluorescence and hyperfluorescence around the macula, which created a bull's-eye pattern in the right and left eyes (Figures 2a and 2b, respectively). The rings extended into the temporal and nasal arcades in both eyes.

The pigmentary retinopathy of both eyes revealed through the fundus images increased the suspicion of BBS. The patient's aunt and grandmother were questioned further regarding any health problems the patient may have had, but both denied any issues. The patient's aunt and grandmother were educated that the decreased vision was likely due to the retinal findings, and a new glasses prescription was not provided as vision was unable to be improved with lenses. The patient was referred to the University Eye Center's retina clinic for further evaluation and management.

Second Visit: Retinal Evaluation

At the retinal evaluation three months later, the patient was accompanied by her teacher and grandmother. The grandmother denied any changes to vision, ocular health, and systemic health since the last



Right Eye

Color	Contrast	Right	Wrong	Total
Red	1	0	5	5
Grn	1	0	5	5
Blu	1	0	5	5

Left Eye

Color	Contrast	Right	Wrong	Total
Red	1	0	5	5
Grn	1	2	3	5
Grn	2	0	1	1
Blu	1	0	5	5

Figure 3. *Rabin cone contrast test; reduced for all colors in both eyes*

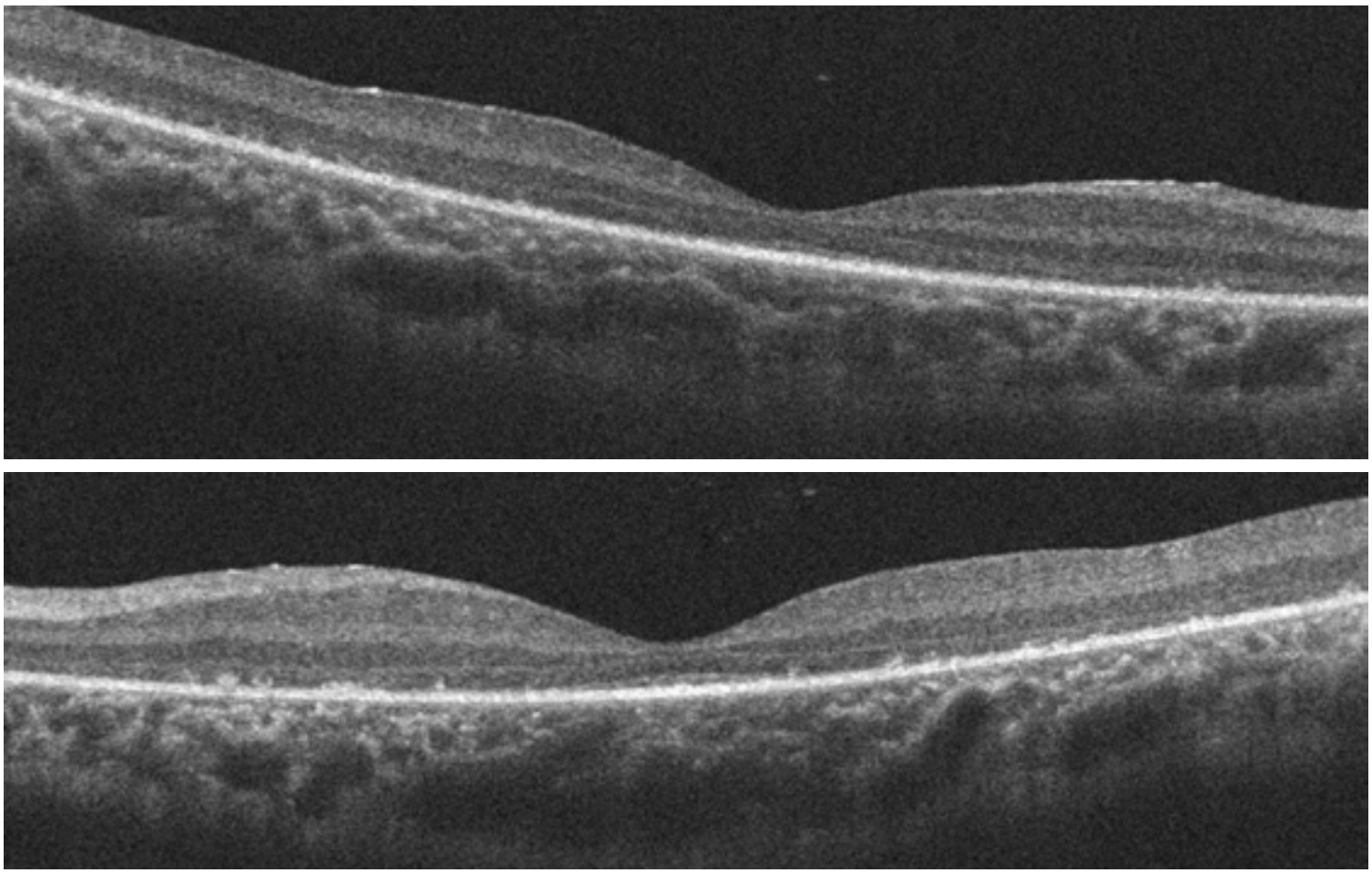


Figure 4. a) *OCT of the macula of the right eye displaying an extinguished PIL parafoveally and minimally present PIL subfoveally*
b) *OCT of the macula of the left eye displaying an extinguished PIL parafoveally and minimally present PIL subfoveally*

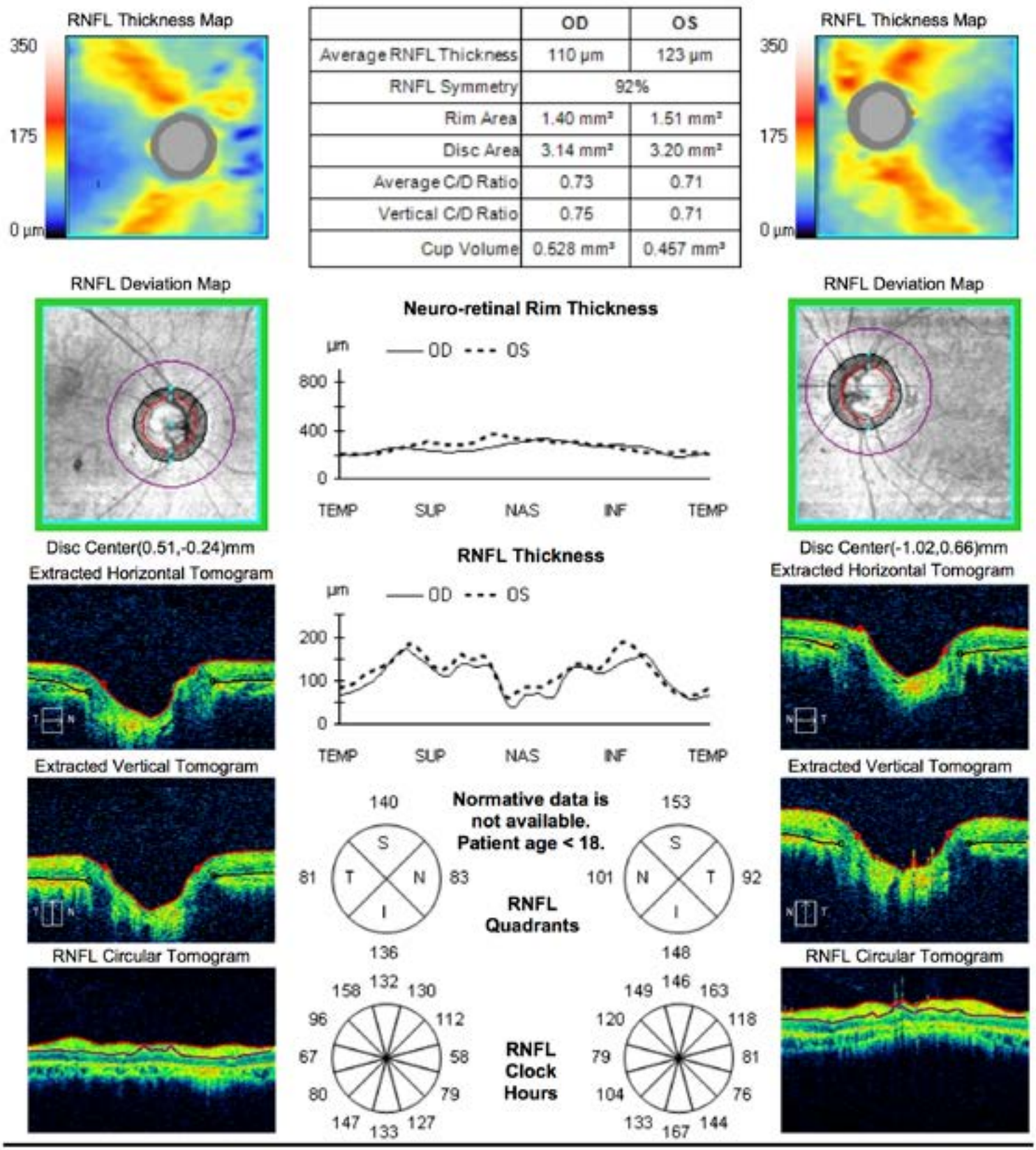


Figure 5. *OCT RNFL displaying thickened RNFL of both eyes*

visit. The BCVA was 20/200 in the right and left eyes. The dilated fundus exam was repeated, and additional tests were conducted.

The Rabin cone contrast test (Figure 3) was performed. This displayed absent color vision in the right eye, while the left eye had some sensitivity to green only. However, the results were only fairly reliable due to the patient's reduced ability to provide reliable subjective responses. Optos fundus photos with fundus autofluorescence were repeated and revealed stable findings in both eyes.

Cirrus optical coherence tomography (OCT) scans of the macula in the right and left eyes were performed (Figures 4a and 4b, respectively). The photoreceptor integrity line (PIL), also known as the ellipsoid zone, in both eyes was extinguished parafoveally and attenuated subfoveally. The choroid was highly hyper-reflective due to the thinner retina in both eyes.

Cirrus OCT scans of the retinal nerve fiber layer (RNFL) were taken (Figure 5), and as the patient was less than eighteen years old, there was no normative database in the Cirrus system. When the patient's values for average RNFL thickness of 110 µm and 123 µm in the right and left eyes, respectively, were compared to norms developed for healthy children by Al-Haddad et al.,[7] they were found to be thicker than the average of 98 µm for the patient's respective age group. Almost all quadrants were thicker relative to the norms.

The ocular findings of decreased vision, nyctalopia, decreased color vision, depigmentary changes in the posterior pole, optic nerve head pallor, attenuated arteries, thickened RNFL, and diminished PIL but absent bone spicules were consistent with atypical RP.[8,9] The atypical RP is likely associated with BBS due to the accompanying developmental delays, polydactyly, and central obesity.[8] The patient's grandmother and teacher were educated on the diagnosis and findings. They were informed of the progressive nature of the condition and poor visual prognosis. The patient was referred for a low vision evaluation and social services at the University Eye Center and, if available, at the patient's school as well.

Discussion

BBS is a syndrome that has very diverse systemic involvement and can initially present to any specialty.[3] This syndrome presents with a widespread spectrum of features but includes a specific pentad of characteristics: pigmentary degeneration of the RP type, obesity, hypogonadism, polydactyly, and mental deficiency.[8] The clinical diagnosis is based on four out of five of these features.[2] However, recent literature has suggested renal involvement to be a sixth component of the syndrome.[8] Other components that are found to be associated with the syndrome include deafness, speech disorder, brachydactyly, syndactyly, diabetes mellitus, ataxia, heart defects, and short stature.[3,8] BBS can also be diagnosed by genetic testing for certain mutations.[4]

One of the most important features of BBS is the retinopathy. This commonly presents as an atypical RP due to early macular involvement and depigmentary changes,[10] although there have been reported cases of various types and severities of pigmentary retinopathies found with BBS, including RP sine pigmento, retinitis punctate albescens, and in some cases, typical RP.[11] There are even some reported cases of cone-rod and choroidal dystrophies.[11]

RP is a progressive rod-cone retinal dystrophy caused by the degeneration of photoreceptors and retinal pigment epithelium cells in the eye.[12] Clinical diagnosis of RP is based on multiple characteristics. Fundus changes include a waxy, pale optic disc, attenuated arteries, and for typical RP, dark bone spicule pigmentary changes in the posterior pole. The RNFL is initially thickened in patients with RP but gradually decreases over time.[13] This thickening is postulated to be due to the proliferation of fibrous astrocytes and edematous residual RNFL.[14] There are also reduced or absent electroretinogram (ERG) amplitudes due to damage to the photoreceptors, starting with rods then affecting cones. This can be further visualized on an OCT scan by the loss of the PIL and a granular appearance of the retinal pigment epithelium (RPE) perifoveally, which gradually extends subfoveally.

Differential diagnoses for atypical RP in BBS include other conditions also associated with ciliary dysfunction with associated pigmentary retinopathies. Due to the ciliary dysfunction, these conditions share similar characteristics to BBS. One such condition is Leber congenital amaurosis, which is associated with very early onset visual impairment that presents with an extinguished ERG.[4] This differs from RP, which will still display some cone function early on. In addition, Alström syndrome is associated with a cone-rod dystrophy, where cone dysfunction precedes rod dysfunction.[4] On the other hand, retinopathy in BBS is commonly a rod-cone dystrophy, where rod dysfunction precedes cone dysfunction. Also, polydactyly does not manifest in either Leber congenital amaurosis or Alström syndrome.[4,6]

If there is no polydactyly present at birth, the age of diagnosis of BBS is often related to the number of symptoms caused by the retinal changes. Distinct

symptoms as described by the patient should increase suspicion of retinal changes characteristic of RP. These symptoms start in childhood and comprise gradual visual loss and impaired night vision, followed by photophobia and color vision loss.[12] As the retinal degeneration progresses, the visual impairment will impair activities of daily living.[12]

Unfortunately, there is no cure for RP, and therapy involves the management of symptoms to improve quality of life and functional ability.[15] An evaluation for low vision aids and services is crucial to maximize the existing vision. Some low vision devices that can be used are electronic ones that magnify and convert text to voice. Stand or dome magnifiers for increased stability and ease of use are especially helpful for those with poor muscle coordination or who are mentally disabled. Due to peripheral vision loss, mobility and scanning training is recommended during the early stages of RP. Tints, portable lighting, and keeping the home well lit are helpful in nyctalopia management.

For younger patients like the one described, the school must be made aware of the visual impairment and provide accommodations, such as a teacher for the visually impaired. Social services may help patients and families of patients obtain accommodations and prepare for the challenge of the poor visual prognosis.[16]

There is ongoing research on other therapeutic implications for BBS, especially for RP. One is the Argus II retinal prosthesis system, which is approved by the United States Food and Drug Administration and can restore some visual function in blind patients with severe RP.[17] The device bypasses the photoreceptors and provides extracellular electrical stimulation to the bipolar or ganglion cells.[18] The device has been shown to improve certain aspects of vision, such as increasing contrast and providing visuals of rudimentary shapes and movement, so that the patient can perform certain daily activities with greater ease.[17,18]

As oxidative stress has been proposed to contribute to the death of photoreceptors, there have been multiple randomized clinical trials on the use of multivitamin and mineral supplements to slow down this progressive damage. Supplementation with vitamin A dosed at 15,000 International Units per day is commonly trialed due to the key role in rod function and dark adaptation; however, there have also been reported uses of vitamin D, lutein, and docosahexenoic acid as well.[19] Unfortunately, whether or not progression of the visual field, visual acuity, and ERG findings is prevented or slowed down by additional multivitamin and mineral intake is still controversial.[19]

Additionally, gene therapy, gene editing, and retinal gene replacement are also currently being explored.[4] Further research in understanding the function of BBS proteins and their role in ciliary function will likely provide better diagnosis, management, and therapeutic opportunities in the future.[5]

As BBS is a multisystem disorder, it is crucial that patients with this syndrome be referred to other specialties, such as cardiology and nephrology, to rule out possible life-threatening manifestations, including heart defects and renal failure.[20] These patients should be referred for management of weight, diabetes, hypertension, and metabolic syndromes.[4]

Conclusion

This case depicts an example of how a detailed case history and complete patient observation should not be overlooked. Although eye care providers are the experts in ocular health, it is important to care for the patient as a whole. A multitude of conditions have accompanying ocular manifestations, and there are many instances when eye care practitioners can be the first to detect them. In turn, this can accelerate the proper treatment and management required for these patients to prevent life-threatening consequences.

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