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Clinical characteristics and ultra-widefield fundus image analysis of two siblings with Bardet-Biedl syndrome type 1 p.Met390Arg variant

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ABSTRACT

Purpose: To present the case of two siblings with a genetic diagnosis of Bardet Biedl syndrome (BBS) type 1, yet different clinical profiles and disease manifestations.

Observations: Sequencing analysis revealed a p.Met390Arg pathogenic variant in the BBS1 gene of both patients, as well as several additional variants of uncertain significance Patient 1 was 41 years old, had three primary (cone-rod dystrophy, hypogonadism, and truncal obesity) and three secondary (arterial hypertension, strabismus, and astigmatism) BBS features. He also had insulin resistance, as well as low levels of total testosterone and cortisol. Patient 2 was 43 years old, had two primary (cone-rod dystrophy and truncal obesity), and four secondary (arterial hypertension, diabetes mellitus, strabismus, and astigmatism) BBS features. Both patients had severe maculopathy; however, patient 1 had bone-spicules that extended up to the mid-periphery, in a perivenular pattern, and significant vascular attenuation with "ghost vessel" appearance towards the temporal periphery, a feature that was absent on patient 2.

Conclusions and Importance: The intrafamilial phenotypic variability among our patients supports the hypothesis that BBS is a disease with genetic, hormonal, and environmental triggers interacting to produce phenotypic variability. Although our report may not establish a definite relationship between environmental and genetic influences, their role should be explored in future studies.

1. Introduction

The Bardet-Biedl syndrome (BBS) is an inherited, ciliopathy disorder with a heterogeneous spectrum of genetic and phenotypic manifestations, primarily including retinitis pigmentosa, polydactyly, truncal obesity, cognitive impairment, hypogonadism in males, and renal anomalies.[1–6] Four of these primary features or three primary and two secondary features, such as diabetes mellitus (DM), hypertension (HTN), hypercholesterolemia, reproductive abnormalities, strabismus, astigmatism, congenital heart disease, and hepatic fibrosis are required for a BBS diagnosis.[1,2,5–7]

BBS has been traditionally described as an autosomal recessive disorder. Currently, 25 genetic variants have been implicated in BBS, with eight of these gene proteins (BBS1, BBS2, BBS4, BBS5, BBS7-9, and BBS18) known to form a protein complex required for ciliary function.[1–3,7] The BBS1 gene and its most common p.Met390Arg variant, have been associated with a broad spectrum of ocular and systemic manifestations as compared to other BBS genotypes.[3,4,8–10]

Several theories have been proposed to explain the phenotypic heterogeneity among BBS patients. Researchers have suggested that patients with BBS may have a triallelic pattern of inheritance.[1,2,8] Furthermore, it has been recently suggested that the phenotypic differences reported among patients with similar genotypes might reflect the role of environmental influences in the manifestations of BBS.[11] However, the mechanisms leading to the phenotypic spectrum among patients with BBS still remain incompletely understood.

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We herein present the case of two siblings with a genetic diagnosis of BBS1 p.Met390Arg variant, yet different clinical profiles and disease manifestations.

2. Case reports

2.1. Case 1

A 41-year-old male with a history of IRD presented for a routine ophthalmic evaluation. The patient had a past medical history of surgically corrected strabismus, bilateral retinitis pigmentosa, hyperlipidemia, HTN, insulin resistance, severe obstructive sleep apnea/hypopnea syndrome with significant hypoxemia, multinodular goiter, hypogonadism, and sinusitis. He denied parental consanguinity or having toxic habits. Physical examination revealed goiter, hypogonadism, truncal obesity, and a body mass index (BMI) of 42.7. Laboratories were remarkable for low levels of total testosterone (1.57 ng/mL) and cortisol (0.10 μg/dl); normal levels of TSH (0.50 μIU/mL) and creatinine (1.08 mg/dl); and increased levels of VLDL (55.60 mg/dl), LDL (212 mg/dl), cholesterol (314 mg/dl), triglycerides (278 mg/dl), and glucose (130 mg/dl).

A comprehensive ophthalmological exam revealed a best-corrected visual acuity (BCVA) of 20/800 in the right eye (OD) and 20/1200 in the left eye (OS), and manifest refraction of +1.25–1.75 × 180, and +1.25–1.00 × 180, in OD and OS, respectively. The patient had bilateral dermatochalasis, allergic conjunctivitis, corneal arcus, and posterior vitreous detachment (PVD). Intraocular pressures (IOP) were normal bilaterally. The fundus examination revealed symmetric bilateral changes. These changes consisted of mild disk pallor and severe macular atrophy with multiple areas of macular retinal pigmented epithelium (RPE) hyperplasia in a bone-spicule arrangement. The bone-spicules extended up to the mid-periphery, particularly in a perivenular pattern. There was significant attenuation of both arterioles and venules, with a "ghost vessel" appearance noted towards the temporal periphery. There were "salt and pepper" changes in the mid-periphery (Fig. 1A).

Bilaterally, the FAF revealed round multifocal areas of hypoautofluorescence involving the macula and the nasal mid-periphery, along with peripapillary hypoautofluorescence. Otherwise, there was granular hypoautofluorescence posteriorly that evolved into a granular pattern of hyperautofluorescence towards the mid-periphery (Fig. 1C). The macular OCT showed bilateral foveal atrophy and significant disruption of the outer retinal layers (Fig. 1E). The full-field ERG examination revealed no recordable scotopic and photopic responses and diminished flicker responses and oscillatory potentials.

Genetic testing results showed a pathogenic homozygous missense variant c.1169T > G (p.Met390Arg) in which methionine is replaced by arginine at codon 390 of the BBS1 protein. The patient had seven additional variants of unknown significance (VUS) at the BBS9, CDH23, CNNM4, PEX10, PEX26, RLBP1, and RP1 genes.

2.2. Case 2

A 43-year-old male with a history of IRD presented for routine ophthalmic evaluation. The patient had a past medical history of HTN, severe obstructive sleep apnea/hypopnea syndrome with significant hypoxemia, fatty liver infiltration, hepatomegaly, and insulin-dependent DM type 2. He denied parental consanguinity or having toxic habits. Physical examination revealed hypertension (154/101 mmHg), truncal obesity, and a BMI of 37.2. Laboratories were remarkable for increased levels of AST (49 IU/L), ALT (81 IU/L), VLDL (41 mg/dl), LDL (139 mg/dl), cholesterol (217 mg/dl), triglycerides (205 mg/dl), and glycosylated hemoglobin (7.5%); and a normal creatinine (0.96 mg/dl).

A comprehensive ophthalmological exam revealed a BCVA of 20/630 OD and 20/300 OS; the manifest refraction was: −0.50–1.00 × 160, and -0.50–0.50 × 180, in OD and OS, respectively. The IOP was normal in both eyes. The ocular alignment was remarkable for esotropia. The fundus examination findings where symmetrical bilaterally; it was

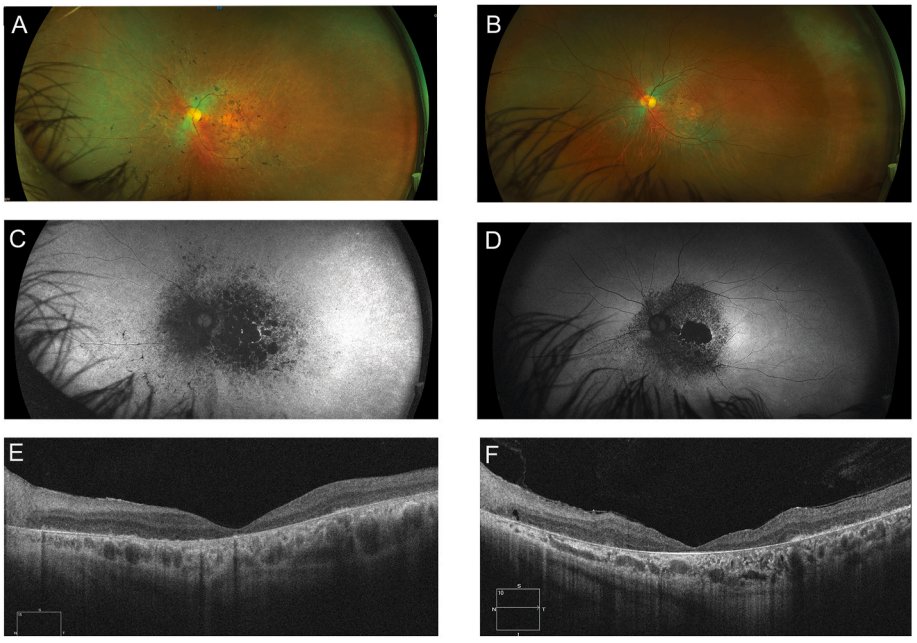

Fig. 1. Ultra-widefield color fundus photographs and fundus autofluorescence (FAF) images, and optical coherence tomography (OCT) of both patients' left eye. A. Color fundus photo of Patient 1, revealing, mild disk pallor, severe macular atrophy with multiple bone-spicules that extend up to the mid-periphery, particularly in a perivenular pattern. There is significant vascular attenuation with a "ghost vessel" appearance noted towards the temporal periphery. There are "salt and pepper" changes in the mid-periphery. B. Fundus photograph of Patient 2 reveals healthy disk appearance, central geographic atrophy, surrounded with less profound macular atrophy that extends inferonasally. Very few bone-spicules are noted within the macula. There is very mild vascular attenuation within the posterior pole. C. The FAF image of Patient 1 shows multiple round areas of hypoautofluorescence involving the macula, nasal mid-periphery, and peripapillary area. Note the granular pattern of hyperautofluorescence extending towards the mid-periphery. **D**. The FAF image of Patient 2 reveals mild peripapillary hypoautofluorescence as well as a prominent central area of geographic hypoautofluorescence that has several smaller satellites of round hypoautofluorescence all within the posterior pole. Granular hypoautofluorescence is present in the remaining macula and extending inferonasally. Macular OCTs of Patient 1 (E) and Patient 2 (F) revealing foveal atrophy and marked disruption of the outer retinal layers. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

remarkable for normal disk appearance, posterior vitreous detachment, and a central area of geographic atrophy, surrounded with less profound macular atrophy that extended inferonasally towards the mid periphery. There were very few areas of RPE hyperplasia in a bone-spicule pattern, all confined within the macula. There was very mild vascular attenuation, which also was limited to the posterior pole (Fig. 1B).

Bilaterally, the FAF revealed mild peripapillary hypoautofluorescence as well as prominent central areas of geographic hypoautofluorescence. There were several smaller satellites of geographic hypoautofluorescence noted OD inferiorly, and inferiorly and nasally OS; all these satellite areas of hypoautofluorescence were relatively few and limited to the posterior pole. Otherwise, there was granular hypoautofluorescence in the macula that significantly extended to a milder degree, yet symmetrically on both eyes. There was a faint edge of hyperautofluorescence, surrounding the hypoautofluorescent areas, save inferonasally (Fig. 1D). The macular OCT showed revealed atrophy of the outer retinal layers, most prominent centrally and temporally, in particular within the areas of geographic atrophy (Fig. 1F). The full-field ERG revealed barely recordable scotopic and photopic responses, along with diminished flicker responses and oscillatory potentials.

Genetic testing results revealed the same BBS1 variant (p.Met390Arg) as his brother (Patient 1). The patient had four additional VUS at the CDH23, CNNM4, PEX26, and RP1 genes. The Table 1 depicts a comparison of the main ophthalmic, systemic, and genetic findings between the two siblings (Patient 1 and 2).

3. Discussion

Many genetic variants have been implicated in the phenotypic heterogeneity associated with BBS.[1–3,7] The BBS1 gene and its p.Met390Arg variant have been commonly described among patients with the syndrome.[4,7,9]

Previous studies have revealed a broad spectrum of ocular and systemic manifestations among patients with BBS1.[3,4,9,10] Recent genotype-phenotype correlations have associated the BBS1 genotype with milder systemic manifestations, including lower rates of renal anomalies, learning disabilities, hypogonadism, and truncal obesity.[2,3,11] Despite these associations, individual predictions about symptomatic manifestations based on genetic profiles still remain a challenge due to the variable expressivity of BBS.[11]

Several theories have been proposed to explain the phenotypic variability among BBS patients. One theory has been associated with a triallelic pattern of inheritance in which the BBS1 gene has been implicated.[1,2] In this pattern of inheritance, the phenotype could be modified by a third mutation, which could be BBS or even neutral variants.[1] The role of variants of uncertain significance (VUS) still remains controversial due to its clinical unpredictability.[12] However, some experts argue that exome based approaches for diagnosis of genetic diseases are beneficial.[12,13] They enable the discovery of potentially significant variants that could provide valuable information about genetic disorders.[12,13] In addition to genetic influences, other researchers have suggested that the phenotypic variations reported among BBS patients within the same families and with the same genotypes might reflect the role of environmental influences in the manifestations of the disease.[11]

The role of hormones in the progression of ocular diseases is a recent and ongoing debate. Estrogen, progesterone, and androgen receptors have been found in various parts of the eye, including the retina.[14] Recent studies have suggested that estrogen derivatives might have neuroprotective effects in the retina under conditions of stress.[14–16] Furthermore, estrogens appear to play a role in the progression of Leber hereditary optic neuropathy (LHON).[16] Although studies have also suggested that progesterone and testosterone might have protective effects in the retina, their roles have been less frequently studied and require further investigation.[14,15] Other researchers have found that insulin receptor-mediated signaling in the retinal pigmented epithelium regulates photoreceptor function.[17]

The two siblings in this case report had the same p.Met390Arg pathogenic variant, yet different clinical profiles and phenotypes. Both siblings had four identical genetic variants (CDH23, PEX26, CNNM4, RP1). However, patient 1 had three additional genetic variants (PEX10, BBS9, and RLBP1), insulin resistance, and low levels of total testosterone and cortisol. Patient 1 was younger yet had worse retinal changes as compared to his sibling (patient 2). He had cone-rod dystrophy, manifested as multiple round areas of atrophy that involved the posterior pole. The patient had bone-spicules in the macula, which extended towards the mid-periphery, particularly in a perivenular pattern. He had significant attenuation of both arterioles and venules, which evolved to a "ghost vessel" appearance towards the temporal periphery.

Furthermore, patient 1 also had different systemic manifestations as compared to his sibling (patient 2). He had three primary BBS features (cone-rod dystrophy, hypogonadism, and truncal obesity) and three secondary features (HTN, strabismus, and astigmatism). Patient 2 was older, had insulin-dependent DM type 2, and had less advanced retinal changes that were more prominent in the macula. He had cone-rod dystrophy with central geographic atrophy. His bone spicules and vascular changes were limited to the posterior pole. He had two primary features (cone-rod dystrophy and truncal obesity) and four secondary features (HTN, DM Type 2, strabismus, and astigmatism). Given the hormonal differences and additional VUS in these two genetically similar siblings, further studies should elucidate the role of hormones and VUS in the phenotypic expression of the syndrome. Some researchers have suggested that in the future, it may be possible to elucidate the cause of variability through analysis that considers the complex interplay of genes, transcription, protein expression, and

Table 1
Comparison of the main ophthalmic, systemic, and genetic findings between the two siblings (patient 1 and patient 2).

Clinical Findings of Patient 1	Clinical Findings of Patient 2
Ophthalmic examination	Ophthalmic examination
BCVA * of 20/800 OD and 20/1200 OS	BCVA * of 20/630 OD and 20/300 OS
Surgically corrected strabismus	Esotropia
Against the rule astigmatism	Against the rule astigmatism
Bilateral cone-rod dystrophy	Bilateral cone-rod dystrophy
Fundus Exam‡	**Fundus Exam‡**
Multiple, round, areas of circular atrophy encompassing the entire macula	A central area of geographic atrophy with some surrounding satellites of atrophy
Multiple bone-spicules extending to the mid-periphery in a perivenular pattern	Few bone-spicules confined to the macula
Prominent attenuation of both arterioles and venules, extending towards the temporal periphery in the form of "ghost vessels"	Very mild vascular attenuation, present only within the posterior pole
Electroretinogram‡	**Electroretinogram‡**
Non-recordable scotopic and photopic responses; diminished flicker responses and oscillatory potentials	Barely recordable scotopic and photopic responses; diminished flicker responses and oscillatory potentials
Systemic manifestations	**Systemic manifestations**
Insulin resistance	Insulin-dependent DM† type 2
Hypertension	Hypertension
Hypercholesterolemia and hypertriglyceridemia	Hypercholesterolemia and hypertriglyceridemia
Truncal Obesity	Truncal Obesity
Obstructive Sleep Apnea/Hypopnea Syndrome	Obstructive Sleep Apnea/Hypopnea Syndrome
Hypogonadism	Fatty liver infiltration with hepatomegaly
Multinodular goiter	
Sinusitis	
Genetic results	**Genetic results**
Pathogenic variant: p.Met390Arg VUS†† at the CDH23, PEX26, CNNM4, RP1, PEX10, BBS9, and RLBP1 genes.	Pathogenic variant: p.Met390Arg VUS†† at the CDH23, PEX26, CNNM4, and RP1 genes.

* BCVA=Best corrected visual acuity; ‡Findings present bilaterally; † Diabetes Mellitus, †† VUS = variants of uncertain significance.

metabolism as part of the phenotypic analysis of BBS patients.[11]

4. Conclusion

We present the case of two siblings with a genetic diagnosis of BBS1 p.Met390Arg variant, yet different clinical profiles and disease manifestations. The phenotypic variability among our patients with the same pathogenic variant could suggest that hormonal influences and additional VUS might be playing a role in their phenotypic differences. Our report further supports the hypothesis that BBS is a disease with genetic, hormonal, and environmental triggers interacting to produce phenotypic variability. Although our report may not establish a definite relationship between environmental and genetic influences, their role should be explored in future studies.

Patient consent

Consent to publish the report of these cases was not obtained. This case series does not contain any personal information that could lead to the identification of the patients.

Declaration of competing interest

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All authors attest that they meet the current ICJME criteria for authorship.

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