Compound Heterozygous Mutations in the BBS-1 Gene and its Clinical Presentation: A Case Report

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Compound heterozygous mutations, where two distinct mutated alleles are present within a particular gene, can give rise to the Bardet-Biedl syndrome (BBS). There is limited evidence suggesting that some compound heterozygotes can present with milder phenotypic characteristics than homozygotes. We report on the clinical characteristics of a 22-year-old Puerto Rican male who was compound heterozygous for the Bardet-Biedl syndrome type 1. Our patient had deteriorating visual acuity since early childhood. Clinical and ophthalmic examination revealed retinal dystrophy, polydactyly, and very mild learning disabilities. No additional systemic complications commonly observed in patients with the BBS were present. Allele-specific testing and DNA sequencing revealed compound heterozygous mutations (M390R and E549X) in the BBS1 gene. Our findings could suggest that patients who are compound heterozygotes for these specific BBS mutations can exhibit milder clinical signs than homozygous patients. [*P R Health Sci J 2021;40:151-154*]

Key words: Bardet–Biedl syndrome, BBS-1, Compound heterozygous

Bardet–Biedl syndrome (BSS) is a pleiotropic genetic disorder inherited as an autosomal recessive disease (1). Clinical findings in patients with the BBS include retinitis pigmentosa; polydactyly; truncal obesity; renal dysfunction; hypogonadism; and intellectual disability (2). However, there is variable expressivity of these signs in patients with the syndrome (1,3).

Retinitis pigmentosa, a type of photoreceptor dystrophy leading to vision loss, is one of the characteristic signs in patients with BBS (4). Fundus examination can reveal retinal pigmentary changes due to migration and proliferation of retinal pigment and epithelial cells or macrophages containing melanin pigment (5). Night blindness is noticed during childhood and is secondary to the initial loss of rod photoreceptor cells (6,7). The progressive loss of photoreceptors leads to the development of blind spots into the characteristic tunnel vision (8). Although there are no proven therapeutic interventions, some individuals with the BBS are given Vitamin A supplementation to help maintain better visual function (9).

Previous studies (10) have reported a prevalence of 69% of post-axial polydactyly among patients with BBS. Truncal obesity has also been reported as one of the principal manifestations of BBS, with a prevalence ranging from 72 to 86% (11,12).

At least twenty-four genes have been associated with BBS (13,14). Previous studies (10,15) have reported that BBS1 is the most common gene associated with this disorder. No significant difference has been reported between the different genes associated with BBS and their phenotype (16).

We report on the milder clinical findings of a Hispanic patient with a compound heterozygous mutation in the BBS-1 gene.

Case Presentation

A 22-year-old male patient with deteriorating visual acuity since early childhood underwent a comprehensive ophthalmic examination. Best corrected visual acuity was 20/80 in the right eye (OD) and 20/40 in the left eye (OS). His cycloplegic refraction was Plano +2.75 x 90 and +0.50 +2.00 x 90, in OD and OS, respectively. Slit-lamp examination was unremarkable. Upon indirect ophthalmoscopy, a pale optic nerve, attenuated vessels, and mid-peripheral bony spicules were observed in both eyes (OU).

The patient underwent a full-field flash electroretinogram (ERG) using corneal contact lens electrodes. Scotopic ERG response to low-intensity blue was flat and hardly discernible when stimulated with high-intensity blue or white light OU. Flicker responses were considerably reduced in amplitude (<22 μV), response latencies were longer than expected (22-30 ms),

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and oscillatory potential was diminished in amplitude (expected > 60 μV) OU. These ERG results were consistent with rapidly progressive rod-cone dystrophies. Stratus optical coherence tomography showed decreased foveal thickness of 156 μm and 192 μm in OD and OS, respectively, and a total macula volume of 9.3 mm3 and 8.3 mm3 in OD and OS, respectively. Humphrey 30-2 perimetry visual field test (Humphrey field analyzer II) showed a field of vision less than 20 degrees rendering him legally blind OU, with a mean deviation (MD) of -25.63 dB and -27.60 dB in OD and OS, respectively ($p<0.5\%$ OU); and a pattern standard deviation (PSD) of 9.05 dB and 7.12 dB in OD and OS, respectively ($p<0.5\%$ OU).

Systemic findings were remarkable for a history of an extra toe on the right foot, which was amputated shortly after birth. In addition, the patient received special education during high school, although he presented with very mild learning disabilities. The patient's body mass index (BMI) was 25.1, and he had a waist width of 80cm. The remaining clinical examination was within normal limits, and no other common BBS comorbidities were identified.

Allele-specific testing and DNA sequencing (Invitae Corporation, San Francisco, CA) were done to detect the pathogenic allelic variant. M390R (p. Met390Arg) and E549X (p. Glu549*) compound heterozygous mutations were found on BBS1.

Studies have shown that 15,000 IU of vitamin A palmitate can slow the progression of early or middle stages of retinitis pigmentosa in adults (3). For this reason, our patient was prescribed vitamin A palmitate 15,000 IU oral dose per day.

Discussion

Six primary features characterize the BBS: retinitis pigmentosa; polydactyly; truncal obesity; renal dysfunction; hypogonadism; and learning disability (2). Secondary features include hypertension, cardiovascular abnormalities, liver disease, diabetes mellitus, subclinical hypothyroidism, among others (2,17). A clinical diagnosis of BBS is made when patients present with either four primary features or three primary plus two secondary features (2). Diagnosis can be confirmed with genetic testing in 80% of patients (18). Our patient presented with only three primary features. Nevertheless, allele-specific testing and DNA sequencing (Invitae Corporation, San Francisco, CA) found compound heterozygous mutations on M390R (p. Met390Arg) and E549X (p. Glu549*), establishing a BBS1 diagnosis.

Although BBS is classically inherited as an autosomal recessive condition, alternate inheritance patterns have been proposed (19–21). Compound heterozygosity, where two different mutated alleles are found within the same gene, has been previously described in BBS patients (21,22). Specifically, compound heterozygotes with M390R (p. Met390Arg) and E549X (p. Glu549*) mutations in BBS1 have been studied within the Puerto Rican population, yet their clinical findings have not been characterized (22). BBS compound heterozygotes have been seen to present with milder phenotypic characteristics than homozygotes (20). Castro-Sanchez and co-workers reported that among their BBS study cohort, BBS1 patients with the homozygous M390R mutation presented a worse ocular phenotype than compound heterozygotes (20). Furthermore, they observed that hypertension was the most prominent systemic characteristic within patients homozygous for the M390R mutation, yet it was absent within the compound heterozygotes (20).

Patients with the BBS eventually become legally blind (1,3,10), as retinitis pigmentosa leads to blindness in most patients with the syndrome (1). Legal blindness is defined as vision worse than 20/200 or a field of vision less than 20 degrees (23). Our patient's ERG was consistent with photoreceptor degeneration. He had a best-corrected visual acuity of 20/80 in the right eye and 20/40 in the left. However, upon visual field examination, our patient had bilateral decreased median deviation scores with visual fields less than 20 degrees. These findings are compatible with those of previous studies on patients with the syndrome (24). In addition, our patient had post-axial polydactyly at birth and received special education during high school even though he had only very mild cognitive disabilities.

Previous studies have reported that not all patients with BBS have truncal obesity (1). Our patient's BMI was 25.1; thus, he was not obese. The width of the patient's waist was within normal limits, measuring 80 cm. However, since additional studies have documented truncal obesity in subjects with the same mutations as our patient, no clear relationship between truncal obesity and compound heterozygotes can be established.

Renal dysfunction remains a leading cause of mortality among patients with the syndrome (25). Although its penetrance is incomplete, most individuals exhibit urinary concentration defects (26). Our patient did not show any signs of renal dysfunction. Beales et al. has reported that cryptorchidism and microphallus occur in up to 13% of male patients with the syndrome (10). However, secondary sexual characteristic development may occur in patients with BBS (1,10,15). Our patient did not have cryptorchidism or microphallus.

The prevalence of intellectual disability was 62% in a cohort of 109 patients (10). Cognitive deficits are characterized by being global; however, it has also been reported that some developmental delays can be specific to a particular area of development (10). The behavioral variant among patients with BBS that exhibit intellectual disabilities ranges from labile behavior to psychosis and autistic spectrum disorders (1). Nonetheless, our patient had only very mild cognitive disabilities.

Our patient exhibited fewer and milder signs of BBS without additional systemic complications. He had two different mutated alleles at M390R (p. Met390Arg) and E549X (p. Glu549*) within the BBS1 gene. This could suggest that patients who are compound heterozygotes for these specific mutations

can present milder systemic comorbidities than those with a homozygous mutation. Further, patients with homozygous mutations can exhibit milder signs than those with a triallelic mutation (27). The absence of homozygosity in our patient could explain why he did not show all the classical characteristics of a patient with the syndrome and why the signs that he did exhibit had a milder presentation.

To our knowledge, this is the first description of the clinical characteristics of a BBS1 compound heterozygous patient in Puerto Rico. Further studies should compare the clinical ophthalmic and systemic findings in patients homozygous for both the M390R (p. Met390Arg) and E549X (p. Glu549*) mutations to those of patients with compound heterozygous mutations within this population.

Resumen

Las mutaciones heterocigotas compuestas, donde dos alelos mutados distintos están presentes dentro de un gen particular, pueden dar lugar al síndrome de Bardet-Biedl (BBS). Existe evidencia limitada que sugiere que algunos heterocigotos compuestos pueden presentar características fenotípicas más leves que los homocigotos. Informamos sobre las características clínicas de un varón puertorriqueño de 22 años que era un heterocigoto compuesto para el síndrome de Bardet-Biedl tipo 1. Nuestro paciente presentaba deterioro de la agudeza visual desde la infancia. La evaluación clínica y oftálmica reveló distrofia retiniana, polidactilia y problemas de aprendizaje muy leves. No se presentaron otras complicaciones sistémicas comúnmente observadas en pacientes con el BBS. Las pruebas específicas de alelo y la secuenciación del ADN revelaron mutaciones heterocigotas compuestas (M390R y E549X) en el gen BBS1. Nuestros hallazgos podrían sugerir que los pacientes que son heterocigotos compuestos para estas mutaciones específicas de BBS pueden tener una presentación clínica más leve que los pacientes homocigotos.

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