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CASE REPORT

Bardet Biedl Syndrome: A Rare Case Series with Ophthalmic and Systemic Presentation

Meenakshi Wadhwani[1], Manoj Kumar[2]

[1]Department of Ophthalmology, Chacha Nehru Bal Chikitsalya, New Delhi, India, [2]Department of Anatomy and Genetics Lab, All India Institute of medical sciences, Delhi, New Delhi, India

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Address for correspondence:
Dr Meenakshi Wadhwani, Assistant Professor and Officer in Charge Ophthalmology, Chacha Nehru Bal Chikitsalya, New Delhi - 110 031, India. Phone: +91-9211543453
E-mail: mkgang08@gmail.com

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Abstract

Bardet-Biedl Syndrome (BBS) is a rare recessive ciliopathic autosomal disorder of humans. The BBS proteins are components of the centrosome and affect ciliary transport, hence the disease falls under the spectrum of "ciliopathies." The involvement of multiple organ systems and associated variable clinical features intensify the need for multidisciplinary approach and management. We hereby are reporting the systemic and ocular findings in three children presenting with BBS.

Background

Bardet-Biedl syndrome (BBS), named after Bardet and Biedl,[1] is a ciliopathic genetic disorder that affects multiple body systems. The first clinical case was reported in 1866 by Laurence and Moon. The main features of BBS include central obesity, retinal pigmentary retinopathy, polydactyly, mental retardation, hypogonadism, and renal abnormalities[1-3].

Case Report

Case 1

An 8-year-old boy presented to the eye outpatient department with complaints of diminution of vision in both eyes at night (nyctalopia) with outward deviation of eyes. There was a history of delayed motor and developmental milestones. He was a product of consanguineous marriage. Mental development was lagging behind the normal range, with an I.Q. of 28.

On ophthalmological examination, his best-corrected visual acuity (BCVA) was 6/36 in both eyes with acceptance of −13.00 D Oculus Dexter (OD) and −15.00 D Oculus Sinister (OS). Anterior segment examination was within normal limits. Prism bar test revealed 30 ΔD of alternate exotropia with OS dominance. Fundus examination revealed disc pallor, bilaterally attenuated vessels, and retinal pigmentary changes of retinitis pigmentosa variety. Electroretinogram revealed diminished response [Figure 1c and d].

Systemic evaluation revealed truncal obesity with distension of the stomach. short, stubby hands and feet, postaxial polydactyly (hexadactyly) of his feet, cryptorchidism, and a microphallus. [Figure 1a and b] The skin of the feet was dry (xerosis). No evidence of hepatomegaly, splenomegaly, skeletal dysplasia and spinal cord abnormality or shoulder abnormality was detected. There was an absence of similar phenotypic characters in other family members.

Case 2

Another 8-year-old girl presented to the eye outpatient department with a complaint of nyctalopia with abnormal eye movements. She was also a product of consanguineous marriage and full-term normal delivery. Pre-natal, natal, and postnatal history was insignificant with the absence of similar phenotypic features in family.

On ophthalmological examination, BCVA was 6/60 in both eyes with acceptance of +2.25 D sphere/−0.50 cylinder (150°) OD and +2.25 D sphere/−1.00 cylinder (10°) OS. Anterior segment examination was within normal limits. Prism bar test had revealed 20 ΔD of alternate esotropia with OS dominance and horizontal jerk nystagmus. Fundus examination showed similar findings of disc pallor, bilaterally attenuated vessels, and retinal pigmentary changes of retinitis pigmentosa variety. Electroretinogram revealed diminished response [Figure 2a-d].

On systemic evaluation, this child also had short, stubby hands and feet, postaxial polydactyly (hexadactyly) of his feet. There was slight incoherence of speech. Truncal obesity was observed with distension of the stomach. Ultrasonography showed no evidence of hepatomegaly, splenomegaly. No skeletal dysplasia and spinal cord abnormality or shoulders abnormality was detected.

Case 3

Another 8-year-old boy presented to the eye outpatient department with complaints of diminution of vision in both eyes at night (nyctalopia). The motor and developmental milestones were delayed. Mental development was lagging behind the normal range, with an I.Q. 32.

On ophthalmological examination, his visual acuity was fixing and following at torchlight in both eyes with acceptance of −3.D Sphere/−2.50D cylinder × 170° OD and of −3.D Sphere/-2.50D cylinder × 10° OS. Anterior segment examination was within normal limits. Fundus examination revealed disc pallor, bilaterally attenuated vessels, and retinal pigmentary changes of retinitis pigmentosa variety.

Systemic evaluation revealed, short, stubby hands and feet, postaxial polydactyly (hexadactyly) of his hand and feet, cryptorchidism, and a microphallus. There was slight incoherence of speech. The skin of the feet was dry (xerosis). Truncal obesity was observed with distension of the stomach. History of family members who had similar phenotypic characters was negative. There was no history of consanguineous marriage [Figure 3a-d and Table 1].

The genetic analysis of all the cases revealed that the direct sequencing of the SNPs [Table 2], BBS1 (rs1136244356), BBS10 (rs766138060) and USH2A (rs915038916 and rs371611777), was negative for any nucleotide variations [Table 3].

The genetic test was not conclusive, however, it was not possible to screen for all the SNPs responsible for BBS; based on the number of primary and secondary phenotypic features. The diagnosis of BBS was made The parents of all the children were counseled and advised regular follow-up to observe whether any progressive ocular or renal changes would develop and for behavioral therapy. Spectacles were prescribed to all children. Alternate eye patching was advised for amblyopia. Strabismus correction was planned after systemic stabilization. The children were referred to dietician and pediatrician for further management. The first patient was also put on testosterone supplementation as per endocrinological consultation.

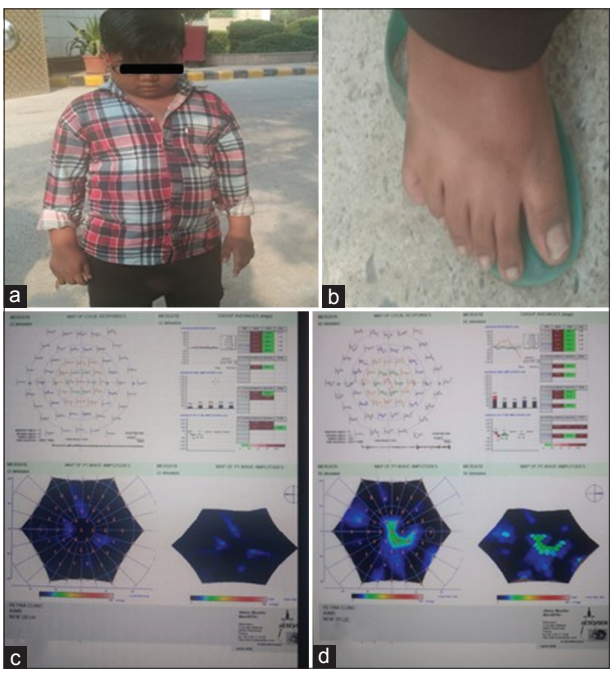

Figure 1: (a) Demonstrating truncal obesity, (b) Postaxial polydactly of left feet, (c) and (d) Electroretinogram showing diminished response in both eyes- Case 1

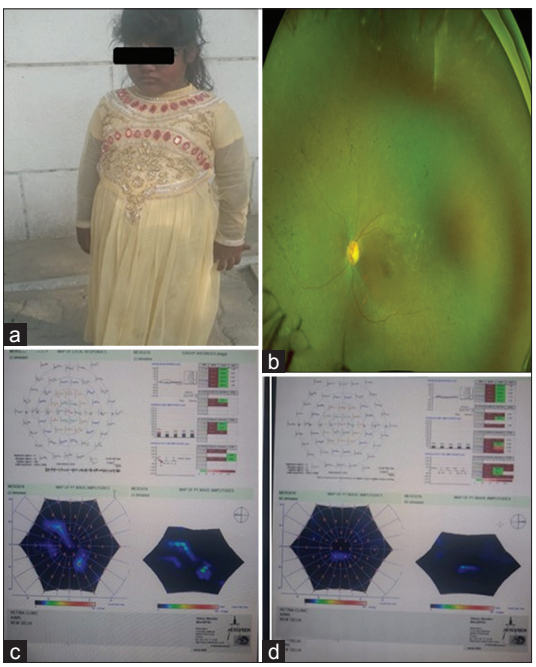

Figure 2: (a) Demonstrating truncal obesity, (b) Fundus photograph showing retinitis pigmentosa variety of retinopathy, (c) and (d) Electroretinogram showing diminished response in both eyes - Case 2

Table 1: Systemic and ocular features in the children suspected with Bardet-Biedel Syndrome

Features	Case 1	Case 2	Case 3
Age/sex	8 year/M	8 year/F	8 year/M
Complaint presented	(1) Diminution of vision at night, (2) Outward deviation of eyes	(1) Diminution of vision at night (2) Abnormal eye movement	(1) Diminution of vision at night
History of consanguinity	+	+	-
Delayed milestones	+	+	+
Systemic features	(1) Short stature (2) Stubby hands and feet (3) Postaxial polydactyly of feet (4) Cryptorchidism (5) Microphallus (6) Xerosis of skin (7) Truncal obesity (8) Speech incoherence (9) No evidence of organomegaly, skeletal dysplasia, spinal cord or shoulder abnormality	(1) Short stature (2) Truncal obesity (3) Stubby hands and feet (4) No hepatomegaly or splenomegaly, no skeletal abnormality (5) Polydactyly of left hand	(1) Short stature (2) Stubby hands and feet (3) Postaxial polydactyly of feet (4) Cryptorchidism (5) Microphallus (6) Xerosis of skin (7) Truncal obesity
Weight	37.2 kg	35.5 kg	33 kg
Height	125 cm	120 cm	120 cm
Body Mass Index	23.8 (>95th percentile)	24.65 (>95th percentile)	22.9 (>95th percentile)
IQ	28	40	32
Ocular features			
BCVA	5/60 in both eyes	6/60 in both eyes	6/36 in both eyes
Refractive error	RE – 13.0 DS LE – 15.0 DS	RE + 2.25DS/–0.50 DC at 150° LE + 2.25 DS/–1.00 DC at 10°	BE + 3.0 DS
Strabismus	30 PD XT	20 PD ET	Absent
Anterior segment	Normal	Normal	Normal
Posterior segment	Pale optic disc, attenuated vessels, pigmentary changes present	Pale optic disc, attenuated blood vessels, pigmentary changes	Pale optic disc, attenuated blood vessels, pigmentary changes
Nystagmus	-	+	-
ERG	Diminished response	Diminished response	Diminished response
Family history	Negative	Negative	Negative

Table 2: The SNPs (*BBS1, BBS10 & USH2A* genes) screened in the patients

Variant ID	Alleles	Conseq. Type	SIFT	PolyPhen	Mutation Assessor
USH2A :rs915038916	G/T	Missense variant	0	0.989	0.792
USH2A :rs371611777	A/C	Missense variant	0.12	0.091	0.156
BBS1: rs113624356	T/G	Missense variant	0.662	0.73	0.605
BBS10: rs766138060	C/T	Missense variant	0.628	0.493	0.659

Table 3: All nucleotide variations found in the *BBS1, BBS10 & USH2A* genes

Patient ID	*BBS1* (rs113624356)	*BBS10* (rs766138060)	*USH2A* (rs915038916)	*USH2A* (rs371611777)
BBS-01	–ve	–ve	–ve	–ve
BBS-02	–ve	–ve	–ve	–ve
BBS-03	–ve	–ve	–ve	–ve

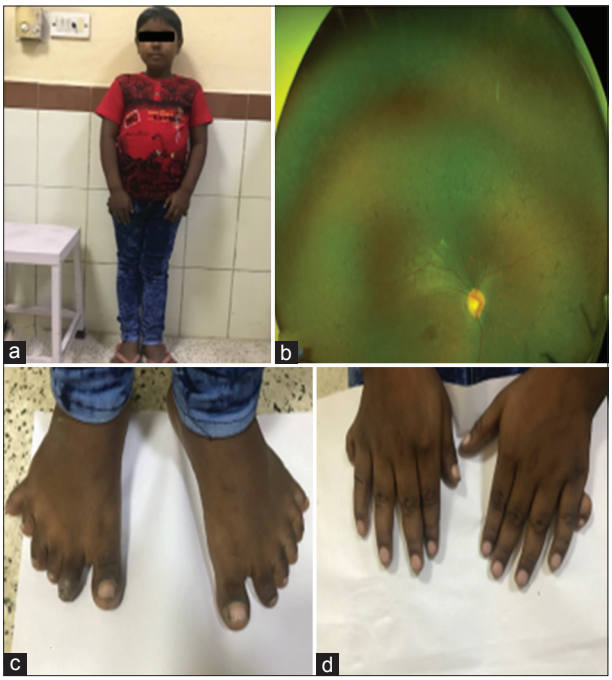

Figure 3: (a) Demonstrating truncal obesity, (b) Fundus photograph showing retinitis pigmentosa variety of retinopathy, (c) and (d) Postaxial polydactly of both feet -Case 3

Discussion

BBS is a rare recessive ciliopathic autosomal disorder of humans. The BBS proteins are components of the centrosome and affect ciliary transport, hence the disease falls under the spectrum of "ciliopathies."[3] The complete spectrum of clinical features is present in only 40–45% of BBS cases.[4] The differential diagnosis for BBS is McKusick–Kaufmann syndrome, Laurence–Moon syndrome, and Biemond–Alstrom syndrome.

The clinical diagnostic criteria for BBS, as proposed by Schachat and Maumenee,[5] are based on the presence of four primary features or three primary and two secondary features as follows:

Primary clinical features

1. Retinitis pigmentosa (rod-cone dystrophy)
2. Obesity
3. Polydactyly
4. Hypogonadism
5. Intellectual disability/cognitive impairment
6. Renal abnormalities.

Secondary clinical features

1. Diabetes mellitus type II
2. Cardiovascular problems
3. Hearing loss
4. Speech deficiency
5. Behavioral problems
6. Craniofacial dysmorphism
7. Short stature
8. Hepatic involvement
9. Eye abnormalities
10. Ataxia
11. Dental and palatal abnormalities
12. Anosmia
13. Hirschsprung disease.

In the current study, there were five primary and two secondary features suggestive of BBS. The global incidence of the syndrome is estimated to be 1:160,000.[6-8] In India, <15 cases have been reported so far.[7] The condition is associated with a high level of consanguinity leading to a higher incidence in some populations, specifically in those that are geographically isolated, such as Newfoundland and Kuwait with disease incidences of 1 in 13,000 and 1 in 17,000 live births, respectively.[1]

The disease was differentiated from McKusick–Kaufmann syndrome[9] in that it occurs only in girls with the main clinical feature of vaginal atresia along with retinitis pigmentosa, thus ruling out its presence in Case2, as the girl in question had normal genitalia. The Laurence–Moon syndrome[10] was ruled out due to the absence of ataxia and syndactyly and the Biemond–Alstrom syndrome[11] was ruled out due to the absence of diabetes mellitus and sensorineural hearing loss.

The management of BBS depends on the associated anomalies. The appropriate counseling of caregivers is necessary. Ocular management includes spectacle prescription, patching therapy, and strabismus correction if present. Testosterone supplements are prescribed to male patients if lowered levels of this hormone are detected. Accessory digits are often nonfunctional and may be excised. The roles of dietician and counselor are especially helpful for the guidance of diet control and to counsel the patient during the stressful time of puberty. A low-calorie and low-protein diet with physical exercise help to control the condition and thus avert multiple health problems, e.g., renal failure.[8]

End-stage renal disease is a common cause of morbidity in BBS in the pediatric population, therefore, a regular assessment of kidney function tests is mandatory.

Conclusion

Due to its rarity and the involvement of different systems, Bardet- syndrome is commonly missed even by specialists. A timely and thorough management plan might allow affected children to integrate better into society and life a fuller life. Furthermore, both parents should undergo genetic counseling, especially those with a history of consanguineous marriages in the family. A close cooperation between ophthalmologists and pediatricians is especially important for the timely diagnosis and treatment of this disease.

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