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Case report

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Clinical heterogeneity of Bardet-Biedl syndrome: A case series

*Hoque AM[1], Islam MH[2], Rahman MA[3], Elahi M[4], Fariduddin M[5]

[1]Ahmad Monirul Hoque, Resident, Department of Endocrinology, Bangladesh Medical University, Dhaka, Bangladesh; [2]Md Hasanul Islam, Resident, Department of Endocrinology, Bangladesh Medical University, Dhaka, Bangladesh; [3]Md Ashiqur Rahman, Resident Physician, Dhaka Medical College Hospital, Dhaka, Bangladesh; [4]Monzur Elahi, Resident, Department of Endocrinology, Bangladesh Medical University, Dhaka, Bangladesh; [5]Md Fariduddin, Professor, Department of Endocrinology, Bangladesh Medical University, Dhaka, Bangladesh.

Abstract

Bardet-Biedl Syndrome (BBS) is a rare autosomal recessive ciliopathy presenting with diverse clinical features, including retinal dystrophy, obesity, post-axial polydactyly, learning disabilities, hypogonadism, and renal abnormalities. Early diagnosis is challenging due to its gradual progression and overlap with other disorders, especially in settings where genetic testing is limited. We report four Bangladeshi cases demonstrating variable phenotypic expressions of BBS. All patients exhibited progressive visual loss, obesity, and polydactyly, along with additional manifestations such as diabetes mellitus, dyslipidemia, hypogonadism, renal impairment, developmental delay, and behavioral issues. Diagnosis was made using Beales' clinical criteria, with each patient fulfilling multiple primary and secondary features. Management required multidisciplinary input from endocrinology, ophthalmology, nephrology, and mental health services, integrating lifestyle intervention, pharmacotherapy, and family counseling. This case series underscores the clinical heterogeneity of BBS, the importance of early clinical recognition, and the need for coordinated multidisciplinary care to optimize long-term outcomes. *[J Assoc Clin Endocrinol Diabetol Bangladesh,* January 2026; 5(1): *66-72]*

Keywords: Bardet-Biedl Syndrome, Retinal dystrophy, Autosomal recessive, Obesity, Post-axial polydactyly

***Correspondence:** Dr. Ahmad Monirul Hoque, Resident, Department of Endocrinology, Bangladesh Medical University, Dhaka, Bangladesh. Email: ahmadhoque77@gmail.com. Contact: +8801880893766.

Introduction

Bardet-Biedl Syndrome (BBS) is a rare autosomal recessive ciliopathy marked by significant clinical variability, posing challenges in diagnosis and management.[1] The disorder typically presents in the first decade of life, with a triad of obesity, postaxial polydactyly, and progressive visual impairment as the earliest manifestations. Several genes associated with BBS affect proteins such as BBSome proteins, basal body-interacting proteins, and chaperonin complex proteins, which are essential for cellular function.[2]

BBS has an estimated prevalence of 1 in 100,000 in Europe and North America, but it is more common among the Bedouin population in Kuwait, affecting approximately 1 in 13,500 newborns.[3] In Bangladesh and other Asian countries, the incidence remains poorly documented.[4] The diagnosis of BBS is made when at least four primary features or three primary features and two secondary features are present.[5] Due to limited access to genetic testing, particularly in developing countries, early diagnosis is difficult. A delayed diagnosis increases the risk of complications, particularly renal damage. Multidisciplinary care, including genetic counseling, is essential for managing BBS and improving outcomes. Early detection is crucial to mitigate morbidity and mortality.

Case 1

A 17-year-old Bangladeshi female, the first child of consanguineous parents, presented with progressive weight gain, poorly controlled diabetes, polydactyly, vision impairment, low IQ, hypothyroidism, and

dyslipidemia. She had a history suggestive of delayed developmental milestones and learning disabilities, with no formal education, although no documentation confirming the developmental delay was available. Similar traits were observed in three paternal uncles, suggesting a genetic cause.

Physical examination revealed obesity (BMI: 31.6 kg/m²), hypertension (140/90 mmHg), and facial abnormalities such as hypertelorism and a depressed nasal bridge. Ocular assessment showed nystagmus and retinal changes, with a dilated fundus examination revealing pale optic discs (Figure-1). IQ assessment using the Wechsler Intelligence Scale for Children (WISC-V) indicated below-average cognitive performance. She met five major and seven minor diagnostic criteria for BBS (Table-I). Laboratory tests revealed elevated HbA1c, dyslipidemia, and renal impairment (elevated creatinine and signs of diabetic nephropathy). Echocardiography showed concentric left ventricular hypertrophy (Table-II). The management plan included insulin therapy, GLP-1

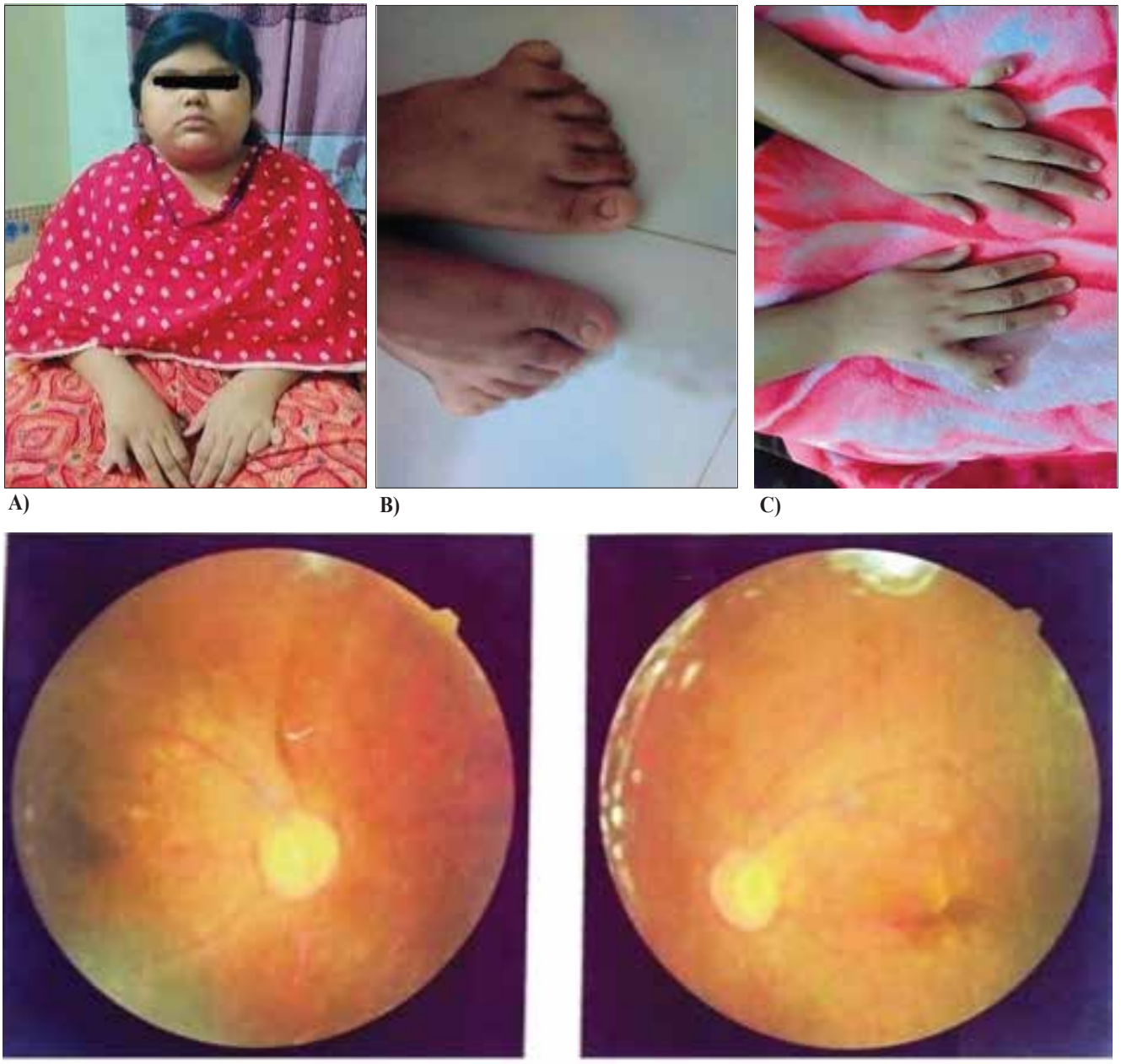


Figure-1: Case-1: (A) Physical appearance, (B) Bilateral lower limb post-axial polydactyly, (C) Bilateral upper limb post-axial polydactyly, (D) Fundoscopy showing waxy optic disc with arteriolar attenuation

Table-I: Presence of diagnostic features in cases of Bardet–Biedl syndrome as per diagnostic criteria

Diagnostic features	Case 1	Case 2	Case 3	Case 4
Primary features				
Truncal obesity	+	+	+	+
Retinitis pigmentosa/retinal dystrophy	+	+	+	+
Polydactyly	+	+	+	+
Learning disabilities	+	+	+	+
Renal malformations	+	+	-	-
Genital abnormalities (female)	-	-	-	-
Hypogonadism (male)	-	-	-	-
Secondary features				
Strabismus/cataract/astigmatism	-	-	-	-
Developmental delay	+	+	+	+
Brachydactyly/syndactyly	+	-	-	-
Behavioral disorders	+			
Diabetes mellitus	+	+	-	-
Polyuria/polydipsia (diabetes insipidus)	-	-	-	-
Left ventricular hypertrophy (LVH)	+	-	-	-
Congenital cardiac abnormalities	-	-	-	-
Hepatic fibrosis	-	-	-	-
Craniofacial dysmorphism	+	-	-	-
Dental crowding/high-arched palate/hypodontia/small roots	+	+	-	-
Hirschsprung disease	-	-	-	-
Ataxia/poor coordination	-	-	-	-
Anosmia	-	-	-	-

receptor agonists, lipid-lowering agents, and antihypertensive medication. Behavioral support was provided for mental health issues, and the guardians were counseled regarding prognosis and follow-up care.

Case 2

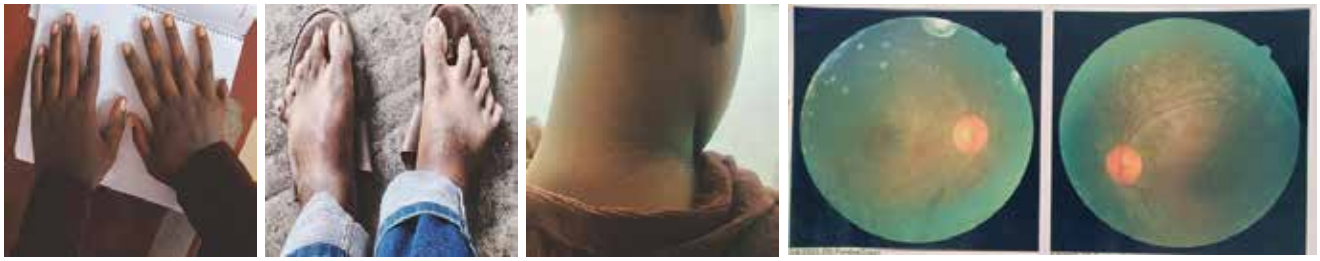
A 16-year-old male, the first child of non-consanguineous parents, presented with progressive weight gain, night vision impairment, and recently diagnosed diabetes. His developmental milestones were delayed, and he had dropped out of high school due to learning difficulties. Physical examination revealed post-axial polydactyly, acanthosis nigricans, and obesity (BMI: 29.7 kg/m²). Fundoscopy showed waxy optic discs with arteriolar attenuation (Figure-2).

Laboratory tests revealed severe hyperglycemia (HbA1c 18.5%), dyslipidemia (triglycerides 554 mg/dL), and renal impairment (creatinine 2.6 mg/dL). Ultrasound showed hepatomegaly with fatty liver and early renal parenchymal disease. A renal biopsy revealed focal and segmental glomerulosclerosis and signs of diabetic nephropathy (Table-II). The diagnosis of BBS was confirmed, meeting six primary and two secondary features (Table-I). Treatment included insulin, linagliptin, and fenofibrate, with additional management for focal segmental glomerulosclerosis.

Case 3

A 14-year-old male with a family history of BBS exhibited progressive vision impairment and learning difficulties since childhood, and no parental consanguinity. He had no issues with hearing, anosmia, or cold intolerance. Examination revealed obesity (BMI 32.3 kg/m²), low IQ, polydactyly, acanthosis nigricans, and a high-arched palate. Fundoscopy showed pale optic discs, but no congenital heart defects or renal issues were noted (Figure-3).

Investigations revealed impaired glucose tolerance, dyslipidemia, and elevated liver enzymes. Hormonal analysis showed low serum testosterone and elevated LH and FSH levels. Ultrasound indicated hepatomegaly with grade III fatty liver (Table-II). His condition was consistent with BBS, with treatment focusing on managing metabolic abnormalities.



A) B) C) D)

Figure-2: Case-2: (A) Upper limb post-axial polydactyly, (B) Bilateral lower limb post-axial polydactyly, (C) Acanthosis nigricans, (D) Fundoscopy showing waxy optic disc with arteriolar attenuation

Table-I: Presence of diagnostic features in cases of Bardet–Biedl syndrome as per diagnostic criteria

Laboratory investigations	Case 1	Case 2	Case 3	Case 4
Hb (g/dl)	10.9	9.5	14.6	13.8
Urine routine and microscopy	Sugar 3+ Protein 3+	Sugar 3+ Protein 2+	Sugar: nil Protein: nil	-
Urine total protein (gm/24 hour)	3.17	3.9	-	-
Serum creatinine (mg/dl)	2.13	2.6	0.83	0.78
S. Electrolyte (mmol/L)	Na-138 K- 3.9	Na-130 K- 4.0	Na-139 K- 3.9	Na-138 K- 4.0
SGPT (U/L)	35	13	60	56
Blood glucose (mmol/L)	Fasting 13.8 Post-prandial 22.5	Random 38.4	Fasting 5.8 2-h OGTT 9.4	Random 6.3
HbA1c (%)	10.5	18.5	-	-
Lipid profile (mg/dl)	TC 140 HDL-C 35 Triglyceride 562	TC 122 HDL-C 23 Triglyceride 554	TC 197 LDL-C 109 Triglyceride 267	TC 178 LDL-C 100 Triglyceride 223
TSH (microIU/ml)	3.49	3.6	3.6	3.7
Serum Testosterone (nmol/L)	-	3.26	1.9	0.08
Serum LH (mIU/ml)	-	5.21	3.3	<0.07
Serum FSH (mIU/ml)	-	10.36	7.9	
USG of whole abdomen	Hepatomegaly with grade II fatty liver; Early renal parenchymal disease	Hepatomegaly; Early renal parenchymal disease, Bilateral slight echogenic kidney	Hepatomegaly with grade II fatty liver	-
Echocardiogram	Concentric LVH		-	-

Case 4

A 7-year-old male, sibling of Case 3, presented with weight gain, learning difficulties, and impaired night vision. He exhibited polydactyly, acanthosis nigricans, and gynecomastia. Fundoscopy revealed typical bony spicule-like pigmentation at the retinal periphery (Figure-3). Routine investigations were normal, except for low testosterone and elevated LH levels. Ultrasound showed hepatomegaly with grade II fatty liver (Table-II).

A) B) C)

D) E)

F)

Figure 3: Cae-3 and 4: (A) Truncal obesity, (B) Bilateral upper limb post-axial polydactyly, (C) Bilateral lower limb post-axial polydactyly, (D) Acanthosis nigricans, (E) Fundoscopy of case 3 showing pale optic disc with arteriolar attenuation, (F) Fundoscopy of case 4 showing pale optic disc with retinitis pigmentosa

Discussion

BBS, a hereditary condition affecting non-motile cilia and central obesity, is clinically identifiable.[6] Syndrome hallmarks include central obesity and polydactyly. It can cause lifelong diabetes, hypertension, and kidney issues, and is usually discovered in early childhood. Sharing genetic material makes consanguineous marriages more prone to causing genetic issues.[7] BBS may result from alterations of several genes that disrupt cilia, which are necessary for cell communication. The clinical complexity and genetic heterogeneity of BBS make

diagnosis challenging and necessitate a complete medical history, physical exam, and genetic testing. Variants of unknown significance may conceal the genetic cause. Due to ciliary dysfunction, BBS damages several physiological systems. This rare, autosomal recessive, heterogeneous, pleiotropic disease affects several physiological systems.[2] Common BBS symptoms include post-axial polydactyly, obesity, retinal dystrophy, learning impairments, renal abnormalities, genitourinary malformations, cardiovascular involvement, developmental delay, diabetes, and strabismus.[8] BBS requires four primary or three primary and two secondary qualities.[9] The clinical manifestations of BBS typically emerge insidiously during childhood, often leading to significant diagnostic delays.[4] A large UK population-based survey highlighted this challenge, reporting an average of nine years from initial symptom onset to definitive diagnosis.[3]

In this series, the first three cases were diagnosed between 14 and 17 years of age, while the fourth was identified at age 7. Given the potential for life-threatening complications and a poor long-term prognosis, timely identification necessitates a high index of clinical suspicion.[4] Retinal dystrophy is a hallmark of the syndrome; although infrequently documented within the first decade of life, it is present in the vast majority of patients by the second decade.[10] Perivascular retinal pigmentary changes in the 'bony spicule' pattern or pigment clumping, optic disc atrophy ('waxy' disc pallor), macular scars with or without epiretinal membranes, and severe retinal artery constriction are fundus abnormalities. Retinal degeneration, myopia, exotropia, and color vision loss are among the symptoms. Fundal and ocular abnormalities were responsible for poor vision in all four cases reported in this series. Case 4 showed typical retinal peripheral 'bony spicule' pigmentation.

BBS's second and third most common features are obesity and limb anomalies such as post-axial polydactyly and brachydactyly. The only birth defect is post-axial polydactyly or syndactyly.[11] Early truncal obesity worsens with age. All our cases were obese and had post-axial polydactyly.

Renal failure causes most BBS morbidity and early death. Cystic renal disease, hypertension, diabetes, and metabolic syndrome can impair renal function.[9] Kidney anomalies include unilateral agenesis, scarring, fetal lobulation, parenchymal cysts, calyceal clubbing, chronic renal insufficiency, renal calculi, and vesicoureteral reflux.[11] In our series, patients 1 and 2 presented with renal impairment. Both exhibited evidence of diabetic nephropathy, while Case 2 also demonstrated biopsy-proven focal segmental glomerulosclerosis.

Parents noticed learning and developmental disabilities in all four cases. Academic failure prompted the first three dropouts. Learning deficits are one of BBS's key diagnostic criteria; however, objective IQ testing only detects a few individuals with mental disability.[4] Men are more likely than women to develop hypogonadism and genital abnormalities (59-98%). Girls with BBS have partial and complete vaginal atresia, absent vaginal and urethral orifices, hypoplastic fallopian tubes, uterus, and ovaries. In contrast, boys show a lack of pubertal development.[11] Cases 2 and 3 in our series did not exhibit age-appropriate pubertal changes and showed biochemical hypogonadism.

BBS individuals with higher insulin resistance and metabolic syndrome rates have higher cardiovascular mortality.[12] Type 2 diabetes affects 6-48% of BBS patients.[13] Cases 1 and 2 had diabetes, case 3 had impaired glucose tolerance. All three have fatty livers and abnormal lipid profiles. Thus, BBS patients require early lifestyle advice from their physicians.[14]

BBS demands a multidisciplinary approach due to its diverse clinical manifestations, requiring coordinated care from pediatrics, neurology, dentistry, ophthalmology, endocrinology, otolaryngology, genetics, cardiology, psychiatry, surgical services, gastroenterology, and nephrology.[15] Setmelanotide, an FDA-approved MC4R agonist, offers a targeted option to address BBS-related hyperphagia and obesity. Additionally, emerging gene therapy strategies aimed at correcting ciliary dysfunction show promise for modifying disease progression, marking an important step toward future disease-modifying treatments. Genetic counseling is essential; however, we could not include the patient's genetic analysis or findings. BBS treatment and management may benefit from genetic testing of BBS mutations.

Conclusions

BBS is a complex genetic disorder that impacts many parts of life. Although BBS is difficult to diagnose, genetic testing has improved the identification of associated mutations. Early diagnosis helps families with the syndrome receive genetic counseling and treatment.

BBS management requires interdisciplinary medical expertise to meet its clinical aspects. BBS has no cure, but gene therapy research offers hope. Researchers, healthcare providers, and advocacy groups are working

together to understand better and manage BBS to improve the quality of life.

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Disclosure

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Data Availability

Any inquiries regarding supporting data availability of this study should be directed to the corresponding author and are available from the corresponding author upon reasonable request.

Ethical Approval and Consent to Participate

Written informed consent was obtained from the patient's attendant. All methods were performed in accordance with the relevant guidelines and regulations.

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