Case Report

A case report on Bardet–Biedl syndrome with disease-causing variant Bardet–Biedl syndrome 1: *De novo* diabetes mellitus

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ABSTRACT

Diabetes mellitus (DM), particularly type 2 diabetes, is demonstrated as one of the common complications and/or a secondary feature in Bardet–Biedl syndrome (BBS) individuals. This case report presents the case of a 15-year-old boy from Andhra Pradesh, India, with BBS, showing polyuria, polydipsia, and elevated blood sugar (400 mg/dL). The patient was diagnosed with BBS at age 11 based on truncal obesity, low intellectual quotient, polydactyly, hypogonadism, and next-generation sequencing. The genetic analysis revealed a homozygous state due to c.195+1G>c in intron 10 of the *FBN3* gene that is associated with autosomal recessive BBS1. On examination, his random plasma glucose (466 mg/dL) and glycated hemoglobin (HbA1C) (>15.0%) were elevated. Consequently, he was diagnosed with a case of *de novo* DM BBS. Ophthalmic evaluation indicated retinitis pigmentosa sine pigmento. Insulin therapy showed improvement in the condition of the patient. The patient was counseled on low-caloric food, physical activity, and regular follow-ups in addition to genetic counseling. The report emphasizes the importance of thorough evaluation following diagnosis to gauge the extent of the disease to prevent complications such as diabetes and renal impairment.

Key words: Bardet–Biedl syndrome, Diabetes mellitus, FBN3 gene mutation, Retinitis pigmentosa

Bardet–Biedl syndrome (BBS) is a multisystemic genetic disorder with varied symptoms such as retinitis pigmentosa (RP) (94%), polydactyly (79%), central obesity (89%), learning disability (66%), and kidney and genital abnormalities (52–59%). BBS is a rare, genetic disorder with an incidence of approximately 1 in 160,000 [1] and is regarded as a type of non-motile ciliopathy. However, consanguinity increases the risk of this inherited disease; hence, this condition is highly prevalent in Newfoundland and Kuwait, where consanguinity is more prevalent within these populations [2]. Twenty-one genes (BBS1–BBS21) associated with this genetic disorder have been identified [3]. The most common genes with disease-causing variants are in BBS1 (23%), BBS10 (15%), and BBS2 (10%) [4]. Owing to genetic diversity and varying clinical presentation, the diagnosis and genetic testing of BBS are challenging. In many low-resource hospitals, genetic testing for BBS may be unavailable or unaffordable. Early diagnosis allows interventions for common complications of BBS: Renal impairment and diabetes mellitus (DM). Type 2 diabetes is often considered a secondary manifestation of this genetic disorder [5]. The rarity and gradual progression of a syndrome can hamper early diagnosis, potentially leading to a higher rate of morbidity and mortality. The control of BBS is supportive, and family genetic counseling is indeed crucial.

In this report, we report a case of BBS *de novo* DM in a 15-year-old male patient from Andhra Pradesh, India, who exhibited polydipsia, polyuria, and elevated blood sugar. The occurrence of osmotic symptoms of DM as a dominant feature of BBS and its management in BBS is being rarely postulated [5-8]. People with BBS appeared to have a high prevalence of insulin resistance and metabolic syndrome based on previous studies involving small and moderately large cohorts [8]. Hence, a better comprehension of the prevalence of DM in people with BBS is significant to develop effective treatments in this population.

CASE REPORT

A 15-year-old boy visited the outpatient department of Medicine, NRI Medical College, Andhra Pradesh, India, in view of elevated blood sugar (400 mg/dL). He was born out of a consanguineous marriage (third generation)

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through a normal vaginal delivery weighing 2.0 kg (Fig. 1). Mother's obstetric history was G4P4L3A0D2. According to the patient's mother, he was obese and had a low intelligence quotient since childhood. The proband's brother is noted to have similar characteristics. During the past 4 weeks, he had polyuria and polydipsia with normal appetite. The patient was diagnosed with BBS at age 11 based on truncal obesity, low intellectual quotient, polydactyly, and hypogonadism and evaluated by next-generation sequencing. The genetic analysis revealed a homozygous state due to c.195+1G>c in intron 10 of the *FBN3* gene that encodes fibrillin-3, a pathogenic variant associated with autosomal recessive BBS1.

The patient was conscious, coherent, and co-operative. Systemic examination revealed obesity (66 kg), postaxial polydactyly in hands and feet (hexadactyly) (Fig. 2), mental retardation, color blindness, and hypogonadism. Examination of the cardiovascular, respiratory, and central nervous systems revealed no abnormality. X-ray of the left wrist joint showed an additional digit lateral to the fifth digit with two phalanges. The proximal phalanx of the 6th digit is seen articulating with the lateral aspect of the body of the 5th metacarpal (Fig. 3).

Complete blood picture and metabolic panel were within normal limits. Urinalysis indicated glucosuria (++++) with normal urine microscopy. The random plasma glucose (466 mg/dL), fasting plasma glucose (420 mg/dL), postprandial blood sugar (153 mg/dL), and HbA1C (>15.0%) were significantly high, indicating a likely diagnosis of diabetes. He was further referred to ophthalmic evaluation to rule out ocular changes related to diabetes.

Ophthalmic evaluation showed nystagmus, stellate posterior subcapsular cataract (right eye>left eye), and macular atrophy in both eyes. Fundus examination portrayed vitreous degeneration, pale optic disc, altered arteriovenous ratio due to arteriolar attenuation, no pigmentary changes over retina, and cellophane maculopathy, which were suggestive of RP sine pigmento (Fig. 4). The echocardiogram revealed normal cardiac structures and function. Ultrasound of the abdomen and pelvis showed no abnormality. On brainstem evoked response audiometry, hearing sensitivity was within normal limits in both ears. All these led to the diagnosis as a case of BBS1 with new onset of type 2 DM (Table 1).

The boy was treated with Mixtard 30/70 injection at 25 units twice daily subcutaneously, and sitagliptin and metformin hydrochloride 50/500 mg orally, along with monitoring of general random blood sugar 3 times daily. The treatment is continued with regular assessment like an outpatient. The patient was counseled on low-calorie food and regular physical activity, as obesity is a risk factor for diabetes. In addition, the patient was advised to have regular check-ups every 3 months with ophthalmologists and nephrologists to prevent further complications.

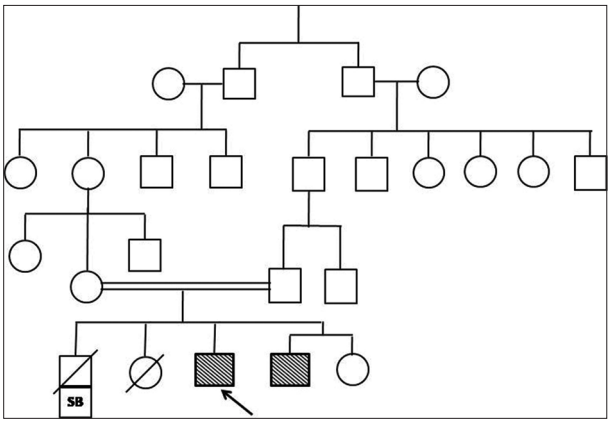

Figure 1: Pedigree of the proband: Arrow indicates the male child

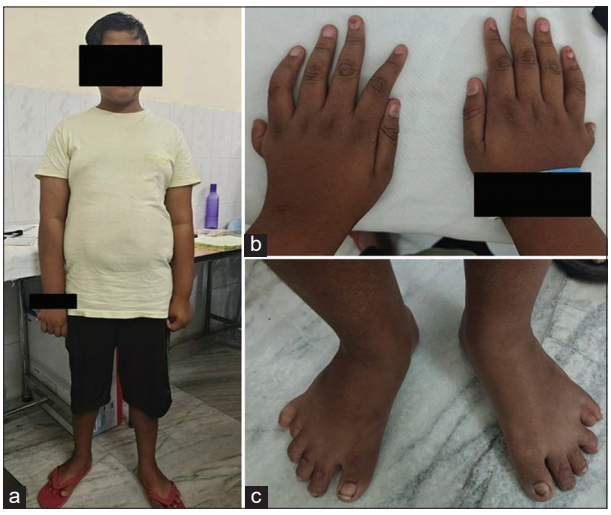

Figure 2: Systemic examination showing (a) truncal obesity, (b) hexadactyly of hands, (c) hexadactyly of feet

DISCUSSION

BBS is an autosomal recessive disorder caused by mutations in the BBS gene family and the *NPHP1*

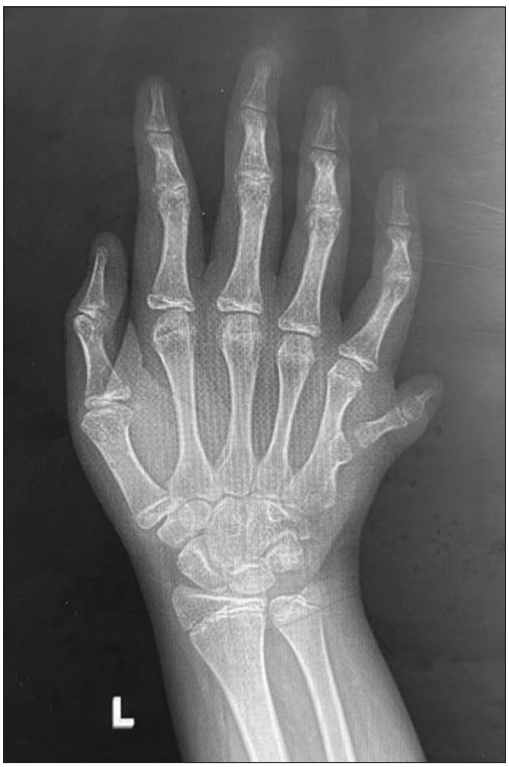

Figure 3: Radiograph (anteroposterior view) of left wrist joint showing additional digit lateral to the fifth digit with two phalanges

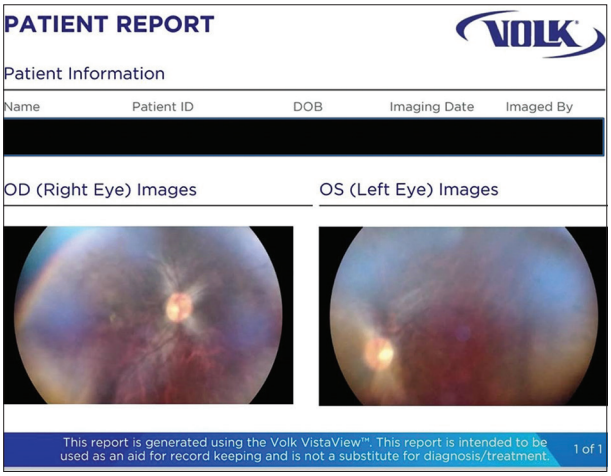

Figure 4: Fundus showing disc pallor, attenuation of arterioles, macular atrophy suggestive of retinitis pigmentosa sine pigmento of both eyes

Table 1: Reported features of BBS and the findings in the present case

Reported features of BBS	Present case findings
Primary feature	
Obesity	Present
Polydactyly	Present
Retinitis pigmentosa/retinal dystrophy	Present
Hypogonadism (male)	Present
Learning disabilities	Present
Renal malformations	Absent
Secondary features	
Brachydactyly/Syndactyly	Absent
Color blindness	Present
Polyuria/polydipsia	Present
Diabetes mellitus	Present
Speech disorders/delay	Absent
Developmental delay	Absent
Strabismus/cataract/astigmatism	Present
Behavioral disorders	Absent
Imbalance/Ataxia/Poor coordination	Absent
Left ventricular hypertrophy/ Congenital cardiac abnormalities	Absent
Hepatic fibrosis	Absent
Craniofacial dysmorphic	Absent
High-arched palate/Dental crowding/ Hypodontia/Small roots	Absent
Hirschsprung disease	Absent
Mild spasticity (lower limbs)	Absent

BBS: Bardet–Biedl syndrome

gene that are involved in the proper functioning of primary cilia. These gene mutations cause ciliopathies, which in turn result in a wide range of multisystemic manifestations in individuals with BBS [2].

The primary clinical features of BBS comprise truncal obesity, polydactyly, learning disabilities, RP, renal abnormalities, hypogonadism in males, and genital abnormalities in females. The secondary features include a broad spectrum of abnormalities such as oral and dental health (hypodontia and microdontia), neurological abnormalities (epilepsy, ataxia, and speech abnormalities), olfactory dysfunctions (anosmia and hyposmia), cardiovascular and thoracoabdominal anomalies (congenital heart disease and Hirschsprung disease), the gastrointestinal system (inflammatory bowel and celiac diseases), and endocrine and metabolic abnormalities (hypothyroidism, polycystic ovary syndrome, and type 2 diabetes) [9]. The clinical diagnosis of BBS can be achieved based on either the presence of four major clinical features or a combination of three major and two minor clinical features.

The majority of symptoms related to BBS become visible after several years of development, making it difficult to diagnose the disease in young children. The average age at BBS diagnosis was 9 years [10]. Here, the patient was diagnosed with BBS based on truncal obesity, low intellectual quotient, polydactyly, and hypogonadism at 11 years, which is considered a delayed diagnosis. Subsequent to diagnosis, it is crucial to conduct a thorough evaluation to gauge the extent of the disease, including renal and liver function tests, urine analysis, blood sugar levels, ophthalmic evaluation, cardiac evaluation, abdominal ultrasound, assessing obesity with body mass index, hearing evaluation and neurological examination that is a major lacuna in the present case. As a consequence, the patient developed DM and RP in due course.

Green *et al*. [11] reported an occurrence of 45% of type 2 DM in BBS patients. The prevailing features of DM in this case were osmotic symptoms (polyuria and polydipsia). BBS patients are 2 times more likely to develop glucose intolerance [12]. In RP, the progressive loss of rod photoreceptors leads to reduced visual acuity and impaired color vision. This loss of cone function is often described as color blindness [13], which is also noticed in the present case. As per the Clinical Registry Investigating BBS Registry, 31% BBS individuals had color blindness. However, the patient did not show any developmental delay, speech abnormalities, imbalance, ataxia, spasticity, dental crowding, congenital heart disease, or hepatic fibrosis. BBS is differentiated from Laurence–Moon syndrome with polydactyly and absence of spasticity; from Ellis–van Creveld syndrome with obesity, hypogonadism, and RP; from Meckel–Gruber syndrome with RP and absence of encephalocele; from Senior–Loken syndrome and Joubert syndrome with polydactyly, obesity, hypogonadism, and genitourinary abnormalities; and from Alstrom syndrome with polydactyly.

Therapeutic options for BBS, based on the findings, include conservative or surgical interventions. The treatment of DM in BBS should comprise exercise, weight reduction, and use of insulin sensitizers, counting metformin and thiazolidinediones [6]. Type 2 DM is the most commonly reported type of diabetes in BBS individuals, and insulin therapy is frequently considered for these individuals when HbA1c is above 10%, or while blood glucose levels consistently exceed 300 mg/dL [14]. The patient had a high level (>15%) of

HbA1c and blood glucose (466 mg/dL). As some patients showed no response to oral antidiabetic drugs in previous studies, this case was treated parenterally.

Obesity, a risk factor for diabetes, is one of the primary clinical characteristics of BBS. Obesity management encompasses lifestyle modifications such as dietary changes and increased physical activity, alongside addressing metabolic syndrome and other related health issues. Periodic consultation with an ophthalmologist is advocated to correct ocular changes. Genetic counseling provides benefits to both the individual with a BBS and their family, and periodic monitoring is essential, especially regarding the reality that their kin who also share similar characteristics.

CONCLUSION

BBS is a rare, genetically diverse ciliopathy that affects multiple organ systems. It is primarily diagnosed according to clinical criteria and can be further confirmed through genetic testing. Early diagnosis of diabetes and coordinated care for BBS are vital for managing complications and improving the quality of life of patients. Avoiding nephrotoxic medications and carefully selecting suitable drugs significantly reduces the risk of kidney damage, thereby lowering the overall morbidity associated with this condition.

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