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CASE REPORT

Case report of twins with Bardet-Biedl syndrome exhibiting a rare mutation in the *TTC8* gene

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ABSTRACT

Bardet-Biedl syndrome (BBS) is a rare, autosomal recessive disorder, resulting from mutations in various genes, including *TTC8*. Abnormal variants in this gene were found in the case of our patients – twin sisters diagnosed with BBS. Next-generation sequencing revealed variants in the *TTC8* gene: c.-104G>A [NM_001288783, rs119103286] and c.635T>C [NM_144596], which are associated with BBS type 8. The variant found in the patients' mother was c.-104G>A, and in the patients' father was c.635T>C, but they did not exhibit any BBS symptoms. Both twins presented several symptoms characteristic of BBS, such as retinopathy, visceral obesity, postaxial polydactyly, renal dysfunction, cognitive impairment, facial dysmorphia, and dental abnormalities. Table 1 compares BBS to other diseases, to facilitate differential diagnosis. Table 2 shows the symptoms of BBS and their frequency of occurrence and Table 3 compares cases of BBS with TTC8 mutation found in the literature.

KEY WORDS:

case report, mutation, ciliopathy, Bardet-Biedl syndrome, TTC8.

INTRODUCTION

Bardet-Biedl syndrome (BBS) is an autosomal recessive multisystem ciliopathy [1]. Cilia are cellular protrusions that arise from the base of the cell [2]. They can be categorised as primary cilia that act like sensors and have signalling functions, and motile – mechanic cilia which generate movement. Defects in primary cilia result in ciliopathies such as BBS [2, 3]. It can be caused by mutations in over 20 different genes that encode proteins of the basal body complex, from which cilia are formed. Bardet-Biedl syndrome is diagnosed clinically when either 4 major features or 3 major and 2 minor features are present [1]. The major features include retinal cone-rod dystrophy (present in 94% of cases). Initially, it manifests by night blindness, followed by progressive peripheral vision loss, a reduction in colour discrimination, and a subsequent loss of visual acuity. The second feature is central obesity, which develops in the first year of life [1]. The mean body mass index (BMI) was found to be 35.7 ±8.0 kg/m² in patients with a mean age of 33.2 ±1.0 years [1]. Nevertheless, the birth weight is typically within the normal range. The third symptom is postaxial polydactyly – the presence of additional digits on the ulnar side of the hand or the fibular side of the foot. The fourth symptom is cognitive impairment, characterised by impairments in verbal fluency, perceptual reasoning, attention capacity, and functional independence. It is notable that features associated with autism spectrum disorders are also frequent, with a prevalence of 77% [1]. Just a quarter of the individuals met the criteria for a diagnosis of intellectual disability. Furthermore, the intellectual functioning of all participants was 1.5 standard deviations below the mean. The fifth symptom is hypogonadism

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TABLE 1. Differential diagnosis of Bardet-Biedl syndrome with characteristic symptoms of each condition

Disorder	Symptoms similar to BBS	Symptoms distinguishing the disease from BBS
Alström syndrome	Cone-rod dystrophy Central obesity Chronic progressive kidney disease Hypogonadism	Absence of polydactyly Preserved cognitive function, progressive sensorineural hearing loss, pulmonary fibrosis and pulmonary hypertension
McKusick-Kaufman syndrome	Postaxial polydactyly Genitourinary malformations	Hydrometrocolpos as one of the main features Absence of retinal disease, obesity and developmental disabilities
Meckel syndrome	Postaxial polydactyly Polycystic kidney disease Genitourinary malformations Hepatic fibrosis	Occipital encephalocele and other central nervous system anomalies as one of the main features; orofacial clefting is common Perinatally lethal
Joubert syndrome	Retinal degeneration Polydactyly Kidney and liver disease	A characteristic triad of molar tooth sign on brain MRI, hypotonia and developmental delay; breathing abnormalities that improve with age are common; eye movement abnormalities and ptosis are common Central obesity, hypogonadism, and genitourinary malformations are atypical.
Senior-Løken syndrome	Retinal degeneration Kidney disease	Absence of obesity, polydactyly, hypogonadism, and genitourinary malformations
Leber congenital amaurosis/early-onset severe retinal dystrophy	Retinal degeneration	Absence of other organ involvement

BBS – Bardet-Biedl syndrome
The table was originally created by RaeLynn Forsyth et al. [1].

and genitourinary abnormalities. In males, the presence of micropenis, small-volume testes, and cryptorchidism may be observed. Female patients may present with anatomical anomalies of the uterus, fallopian tubes, vagina, and urinary tract. Infertility is a relatively common occurrence, although both sexes have been known to conceive children [1]. The sixth symptom is kidney disease, which is highly variable and can include structural anomalies, hydronephrosis, and vesicoureteral reflux. The initial diagnosis of renal disease was made within the first year of life in almost all cases diagnosed by the age of 5 years. The incidence of renal problems is approximately 52%; although it is not the most prevalent symptom, it remains a significant cause of mortality in patients with BBS [1].

Minor features include neurologic abnormalities (mainly developmental delay), anosmia and hyposmia with an abnormal magnetic resonance imaging appearance of the olfactory bulb, hearing loss, eye abnormalities, oral or dental abnormalities (crowding, hypodontia, high-arched palate), cardiovascular and thoracoabdominal abnormalities, gastrointestinal abnormalities, and endocrine or metabolic abnormalities, which are often accompanied by obesity [1]. Additionally, patients may present facial dysmorphia, short stature, and behavioural or psychiatric disorders [1, 2]. The typical symptoms of BBS are summarised in Table 2.

This study presents a description of twin sisters from Europe, specifically Poland, with abnormal variants present in the *TTC8* gene, which is known to cause BBS. The prevalence of the *TTC8* gene mutations in patients presenting with BBS symptoms is estimated to be approximately 2%. The 2 girls demonstrated some of the typical characteristics of BBS and underwent genetic testing [1].

TABLE 2. Collection of symptoms and features present in Bardet-Biedl syndrome along with their frequency of occurrence [3–10]

Feature	Incidence (name of the most prevalent symptom in the group) (%)
Retinal cone-rod dystrophy	94
Abnormal electroretinogram	80–99
Obesity	89
Postaxial polydactyly	79
Intellectual disability	80–99
Hypogonadism and genitourinary abnormalities	59
Kidney disease	52
Dermatologic abnormalities	80.6 (keratosis pilaris)
Hypertension	30–79
Oral/dental abnormalities	Around 50
Gastrointestinal abnormalities	30 (liver disease)
Olfactory dysfunction	47–100
Endocrine/metabolic abnormalities	54.3 (metabolic syndrome)
Short stature	30–79
Nystagmus	30–79
Skeletal muscle atrophy	5–29
Finger syndactyly	5–29
Deafness	5–29
Low-set, posteriorly rotated ears	5–29
Medial flaring of the eyebrow	5–29
Prominent nasal bridge	5–29
Short neck	5–29

TABLE 3. Summary of 21 out of 35 cases of Bardet-Biedl syndrome with a mutation in the *TTC8* gene described in the literature (Medline)

Author	Heritage	Major features						Other features
		Rod-cone dystrophy	Poly-dactyly	Obesity	Hypogo-nadism	Renal anomalies	Cognitive impairment	
Patient 1	Polish	+	+	+	–	+	+	Dental anomalies, hyperopia
Patient 2	Polish	+	+	+	–	+	+	Heart diseases, dental anomalies, hyperopia
Sato *et al*. [15]	Japanese	+	+	+	–	+	–	Abnormal glucose tolerance, exotropia, hypertension, cataract, hemophilia
Ansley *et al*. [16]	Pakistan	+	+	+	+	/	+	Brachycephaly
Ansley *et al*. [16]	Pakistan	+	+	+	+	/	+	Brachycephaly, situs inversus
Ansley *et al*. [16]	Pakistan	+	+	+	+	/	+	Brachycephaly
Ansley *et al*. [16]	Saudi Arabian	+	+	+	+	/	+	Brachycephaly
Ansley *et al*. [16]	Saudi Arabian	+	+	+	+	/	+	Brachycephaly
Ansley *et al*. [16]	Saudi Arabian	+	+	+	/	/	+	Deafness
Ansley *et al*. [16]	Saudi Arabian	+	+	+	/	/	+	Hypospadies
Ansley *et al*. [16]	Saudi Arabian	+	+	+	/	/	+	Asthma
Stoetzel *et al*. [12]	North African	+	+	/	/	/	+	Micropenis
Stoetzel *et al*. [12]	North African	+	+	/	/	+	/	Hydrometrocolpos
Stoetzel *et al*. [12]	North African	+	+	/	/	+	/	–
Harville *et al*. [17]	Turkish	+	+	+	+	–	/	–
Janssen *et al*. [18]	/	+	+	+	–	–	+	Asthma, nasal cephalocele
Janssen *et al*. [18]	Hispanic	+	+	+	+	+	+	Fatty liver, gall stones
M'hamdi *et al*. [19]	Tunisian	+	+	+	+	+	/	Dental anomalies, hypertension
Ullah *et al*. [20]	Pakistan	+	+	+	+	–	+	Clinodactyly
Ullah *et al*. [20]	Pakistan	+	+	+	+	/	+	Clinodactyly
Ullah *et al*. [20]	Pakistan	+	+	+	/	–	+	/
Goyal *et al*. [21]	Indian	+	/	/	/	/	/	Myopia
Schaefer *et al*. [22]	/	+	+	+	+	+	/	/

+ Symptom present
– Symptom absent
/ No data

According to our knowledge, this is the first report in the literature documenting BBS in twins.

CASE REPORT

We present a case of 2 female monozygotic twins, referred to as Patient 1 and Patient 2, both 7 years old. They were delivered at 37 weeks of gestation by caesarean section, during the mother's third pregnancy and second labour. At birth, Patient 1 weighed 2070 g (< 3%) and was 48 cm in length (25%), compared to 3160 g (50–70%) and 53 cm (97%) for Patient 2. Both girls had Apgar scores of 10. Patient 1 exhibited postaxial polydactyly of the left foot, while Patient 2 had bilateral feet polydactyly.

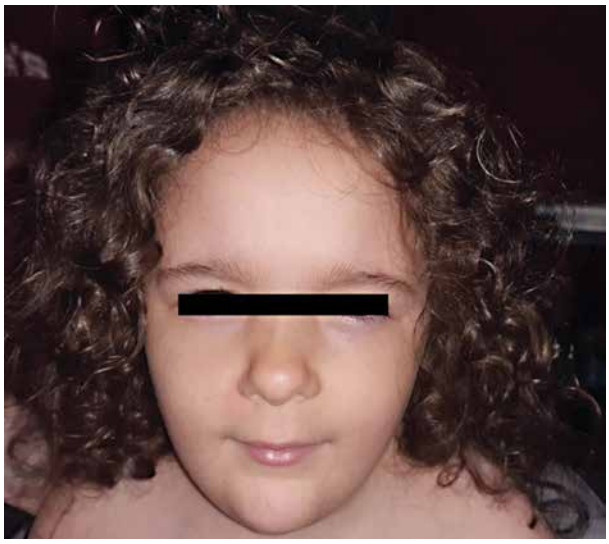

FIGURE 1. Patient 1 with visible facial dysmorphia: broad facial shape, hypertelorism, wide nasal root

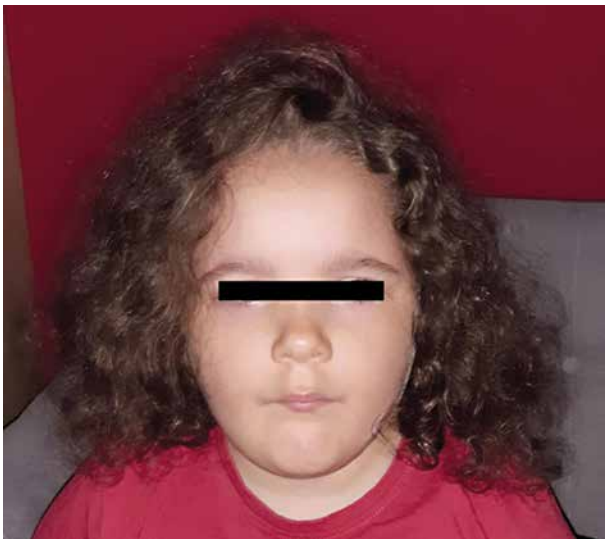

FIGURE 2. Patient 2 with visible facial dysmorphia: broad facial shape, hypertelorism, wide nasal root

Screening ultrasound of the abdomen shortly after birth revealed loss of corticomedullary differentiation, increased echogenicity, and small cysts in both kidneys of both patients. The kidney function was slightly reduced from the first year of life in both children. In Patient 1, the estimated glomerular filtration rate (eGFR) (calculated with Schwartz 3-markers equation and U25 equation) was 66 ml/min/1.73 m^2 at 5 months of age, 67 ml/min/1.73 m^2 at 6 years of age, and 82 ml/min/1.73 m^2 at 8 years of age. In Patient 2, eGFR was 76 ml/min/1.73 m^2 at 5 months of age, then 65 ml/min/1.73 m^2 at 6 years of age, and 82 ml/min1/.73 m^2 at 8 years of age. At 5 months of age, the aforementioned results, in conjunction with the abnormalities observed in renal ultrasound, raised a suspicion of chronic kidney disease (CKD) in both patients. At 6 years of age the diagnosis of stage II CKD was certain. No other abnormalities in laboratory results concerning kidney function were noted. The most recent ultrasonography (2024) of the twins' abdomens showed only a loss of corticomedullary differentiation, with no signs of cysts that were present in the neonatal period. Neither albuminuria nor hypertension was observed. In Patient 2, the urinary tract was examined only in infancy, and a voiding cystogram was performed with normal results. There was no family history of renal disease.

Neonatal echocardiography was normal in Patient 1. However, Patient 2 was found to have a patent foramen ovale (PFO) and mild stenosis of the left main pulmonary artery. Ophthalmologic examination revealed astigmatism in both Patient 1 (–1.5D in the right eye and –1.25D in the left eye) and Patient 2 (–1.5D in both eyes), as well as hyperopia in Patient 1 (+2.0D in both eyes) and Patient 2 (+2.0D in the right eye and +2.5D in the left eye). Fundoscopy showed no abnormalities, but both patients were diagnosed with retinopathy due to night vision deterioration. From the second month of life, both girls showed rapid weight gain and visceral obesity. Physical examination revealed a broad facial shape, hypertelorism, narrow palpebral fissures, wide nasal root, retrognathia, and diastema. Some of these dysmorphisms are visible in Figure 1 and 2. Furthermore, they presented severe intellectual and physical disabilities, including aphasia and autism spectrum, as well as attention deficit, information processing difficulties, and delayed development of memory, compared to their peers. Gynaecological screenings were negative for both siblings. The patients' clinical presentation was consistent with the BBS phenotype; therefore, during hospitalisation Patient 2 underwent genetic testing of the *BBS10* gene, which revealed no pathogenic variants.

At the age of 18 months, the mother funded genome analysis of Patient 2. The *BBS10* gene was analysed by Sanger sequencing of a blood sample and showed no mutations. Next-generation sequencing for less common genes associated with BBS revealed 2 potentially pathogenic heterozygous variants in the *TTC8* gene, associated with BBS type 8: c.-104G>A [NM_001288783, rs119103286] and c.635T>C [NM_144596]. These findings were confirmed using Sanger sequencing. Subsequently, Patient 1 and the parents were screened for *TTC8* mutations by Sanger sequencing. Patient 1 was found to have the same variants as her sister. The mother had the single heterozygous c.-104G>A variant, which was absent in the father, who had the single heterozygous c.635T>C mutation. Despite these mutations, the parents did not exhibit symptoms suggestive of BBS. The mother has a simple cyst in the right kidney, and the father has myopia, astigmatism (0.8D in the right eye), hyposmia and was recently diagnosed with colorectal adenocarcinoma. The patients' 13-year-old brother did not undergo genetic testing. A boy shows sensory integration dysfunction, sensory hypersensitivity, and has been diagnosed with autism; however, he is developing appropriately and does not present a typical BBS clinical image.

Currently, at the age of 7.5 years, Patient 1 weighs 37 kg (97%) with a height of 138 cm (97%) and 19.4 kg/m² BMI, while Patient 2 has a body mass, height, and BMI of 46 kg (> 97%), 142 cm (> 97%), and 22.8 kg/m², respectively. They are under regular follow-up by a nephrologist, neurologist, ophthalmologist, and psychologist.

DISCUSSION

Bardet-Biedl syndrome is a rare pleiotropic ciliopathy characterised by the major typical features mentioned above. Both of the patients reported in our study presented some of the BBS symptoms: retinal dystrophy, excess body weight, postaxial polydactyly, cognitive impairment, developmental delay, astigmatism, hyperopia, hypertelorism, broad nose, mandibular retrusion, and diastema. Additionally, Patient 1 presented PFO and mild stenosis of the left branch of the pulmonary artery.

Some of the symptoms of BBS, like polydactyly in the feet and/or hands, visual problems, renal diseases, and cardiovascular abnormalities, may be present at birth. It is noteworthy that certain abnormalities, such as obesity, cone-rod dystrophy, dental abnormalities, developmental delay, or behavioural/psychiatric abnormalities, which are not present at birth, tend to manifest with age. The average age of onset of BBS is between 4 and 6 years [11].

The syndrome is rare, with a prevalence of 1/125,000 to 1/175,000 in Europe and North America. Consanguinity plays a remarkable role in the incidence of the syndrome, as shown by the Bedouin community in Kuwait, where the incidence of BBS is higher – 1/17,000. First-degree consanguineous marriages are common among families with BBS, ranging from 35 to 48% [11].

Bardet-Biedl syndrome is a genetically heterogeneous disorder. To date, 26 different genes have been identified as potential causes of BBS. The impact of each gene on the disease varies from patient to patient. The patients described in this study exhibited a mutation in the *TTC8* gene, which has been designated as BBS type 8. This is one of the rarest mutations associated with this syndrome. In the literature, the prevalence of *TTC8* gene mutations in this syndrome is described as 2%. Mutations in *TTC8* gene are associated with non-syndromic retinitis pigmentosa and are also considered to be less syndromic with low penetrance of renal abnormalities [1]. However, renal diseases are a relatively prevalent symptom of BBS, present in 52% of patients [1]. In our case, both of the patients showed slightly improved kidney function based on eGFR values (from approximately 70 ml/min to approximately 82 ml/min in 8 years of life).

Substantial clinical variation among families with BBS is recognised, even among patients with the same mutation, suggesting the potential role of modifier genes. These might be other *BBS* genes or unrelated genes that do not cause BBS alone. Supporting this, 3 families have been reported where individuals with 3 mutations at 2 BBS loci show a more severe phenotype. This indicates that variations at one BBS locus can influence the phenotype of mutations at other loci. Extreme cases include disease non-penetrance, where individuals with the disease-causing genotype remain unaffected. An example includes siblings with *BBS2* gene mutations where only one with an additional *BBS6* mutation is affected. These findings suggest complex inheritance patterns, impacting recurrence risk assessments and our understanding of BBS biochemistry [2].

In patients with multiple abnormalities arising from different systems, accurate diagnosis is of critical importance. In the differential diagnosis of Bardet-Biedl syndrome, it is important to consider disorders such as Alström syndrome, McKusick-Kaufman syndrome, Meckel syndrome, Joubert syndrome, Senior-Løken syndrome, and Leber congenital amaurosis/early onset severe retinal dystrophy. These syndromes are caused by genetic mutations that can be confirmed by whole-exome sequencing which is the preferred first-line diagnostic test for patients with multiple congenital anomalies [1].

Stoetzel *et al*. described a cohort of 128 families with at least one member diagnosed with BBS. *BBS8* (*TTC8*) mutations were found in 3 of the families (2%), 2 of them showing homozygous mutations and one showing a heterozygous mutation [12]. Another paper identified a *BBS8* (*TTC8*) mutation in 1% of the examined families, which shows the rarity of this mutation [13]. The most prevalent mutation is BBS1, associated with 23.4% of BBS cases [1]. In northern European individuals, the most common alleles are *BBS1 M390R* and *BBS10 C91LfsX5*, while mutations in *BBS4*, *BBS5*, and *TTC8* are primarily found in patients of Middle Eastern and North African descent [14].

In our report, 2 variants in the *TTC8* gene were identified in both Patient 1 and Patient 2, namely: c.635C>T and c.-104g>A. Testing of the patients' mother revealed only the c.-104g>A variant, and testing of the father showed only the c.635C>T variant.

There is no therapy to prevent multisystem and progressive organ involvement in BBS, necessitating coordinated multidisciplinary care. For cone-rod dystrophy, educational planning should assume future blindness, emphasising Braille, mobility training, adaptive skills, and the use of large-print materials. To manage obesity, a reduced-calorie diet and regular aerobic exercise, adapted for the blind, are recommended, with the support of a helper. Metabolic syndrome and other obesity-related complications should be managed as in the general population. Anosmia or hyposmia require alternative methods to detect dangerous substances. Renal, gastrointestinal, liver diseases, hypothyroidism, and hypogonadism should follow general treatment guidelines, and anatomical abnormalities may need surgical correction [1, 5]. For neurodevelopmental issues, approaches should be individualised. From birth to three years of age, early

intervention programs offer therapies and support. From ages 3–5 years, developmental preschool programs are recommended, with evaluations to develop individualised education plans. For all ages, developmental paediatricians can ensure appropriate services and support. Education plans should be reviewed annually, with vision and hearing consultants included in the team. Children with BBS may benefit from interventions for autism spectrum disorder, such as applied behaviour analysis, tailored to individual needs. Concerns about depression and anxiety, especially in late teens, should be addressed by a paediatric psychiatrist [1].

CONCLUSIONS

Bardet-Biedl syndrome is a rare genetic disorder characterised by a wide range of clinical manifestations. This study documents the first description of BBS in twins. Due to the large number of mutations that can cause the disease, there are many variants that can be associated with different symptoms. We hope that this study, by focusing on the mutation in the *TTC8* gene, will add to the current knowledge of this condition and provide clinicians with useful information.

DISCLOSURE

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4. Conflicts of interest: None.

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