

CASE REPORT

Late diagnosis of Bardet-Biedl syndrome in an 18-year-old patient – a case report and literature review

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ABSTRACT

Bardet-Biedl syndrome (BBS) is a rare, autosomal recessive multi-system ciliopathy. Its diagnosis is based on a constellation of characteristic clinical symptoms that appear in childhood, including kidney defects, obesity, retinal dystrophy, polydactyly, intellectual dysfunction, and hypogonadism.

We present a case of an 18-year-old girl with a postnatal diagnosis of postaxial polydactyly of the feet and hands and bilateral cutaneous syndactyly of the 2nd and 3rd toes, who successively developed most of the typical BBS manifestations. Despite this, the correct diagnosis was made only 3 months before adulthood in our clinic, to which the patient was referred because of suspicion of hypertension. Molecular testing confirmed the clinical diagnosis of BBS (homozygous variant c.619-1G>C in the *BBS5* gene).

The presented case is an example of a delayed diagnosis of BBS. The main reason was the lack of a comprehensive assessment of the multi-system disorders characteristic of BBS.

KEY WORDS:

obesity, polydactyly, ciliopathy, Bardet-Biedl syndrome.

INTRODUCTION

Bardet-Biedl syndrome (BBS) (ORPHA: 110) is a rare, autosomal recessive ciliopathy. It is a pleiotropic disorder triggered by mutations in genes coding proteins of the primary cilium/basal body complex.

Clinical symptoms of BBS include renal abnormalities, truncal obesity, retinal dystrophy (retinitis pigmentosa), polydactyly, intellectual dysfunction, and hypogonadism. Beales *et al.* published diagnostic criteria of BBS based on typical clinical features [1]. However, currently molecular confirmation is the diagnostic tool of choice.

We report on an 18-year-old girl with a typical phenotype of BBS and delayed diagnosis.

CASE REPORT

A girl of Polish descent, a third child of non-consanguineous, healthy parents was born at the 40th week of

an uneventful pregnancy with a weight of 3480 g (75th percentile), a length of 56 cm (> 97th percentile), and a head circumference of 34 cm (75th percentile). APGAR scores were 9 and 10 at 1 and 5 minutes, respectively. The family history, apart from the patient's siblings (the first-term baby was stillborn, and the second sister died at the age of 17 months due to a Wilms tumour) was irrelevant.

After the birth, bilateral postaxial polydactyly of the toes and hands (vestigial fingers in the form of skin processes on the fifth fingers) along with cutaneous syndactyly of the 2nd and 3rd toes were diagnosed. After the age of 2 years, increased appetite and excessive weight gain were observed. At the age of 5 years, vision deteriorated due to myopic astigmatism and alternating divergent strabismus with the predominance of the right eye was found. Spectacle correction was used. Due to increasing obesity unresponsive to diet, the patient was referred to an endocrinologist. Subclinical hypothyroidism was suspected, and treatment with L-thyroxine was temporarily introduced

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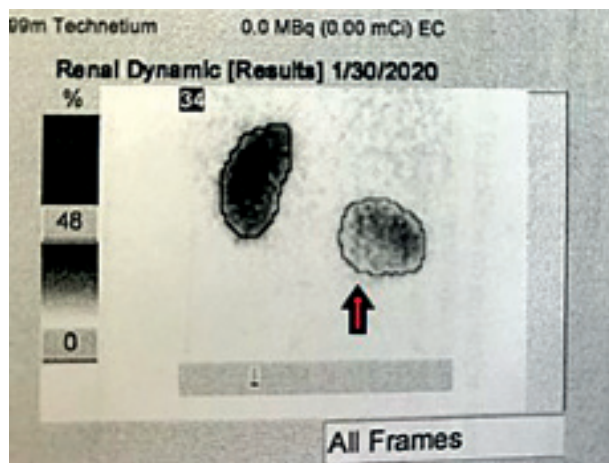


FIGURE 1. ^{99m}Tc-EC renal scintigraphy scan in the presented patient. Note the smaller, rotated, ectopic right kidney with a cortical scar in its lower pole – arrow (Chair and Department of Nuclear Medicine, Medical University of Lublin)

without any clinical effect. At the age of 7 years learning difficulties occurred and mild mental retardation was diagnosed. Three years later ultrasounds revealed ectopy and hypoplasia of the right kidney. Due to the symptoms of metabolic syndrome (glucose intolerance and hyperinsulinaemia) and primary amenorrhoea at the age of 17 years, metformin treatment was started. Genetic testing showed

a normal karyotype and excluded suspected Willy-Prader syndrome. Due to kidney malformation, the patient was referred to a nephrology outpatient clinic, where at the age of 17.3 years, renal scintigraphy was performed. It revealed ectopy and smaller size of the right kidney (83 mm, while the left kidney was 124 mm long) with decreased relative function to 33.3% and the presence of parenchymal defects (blurred outlines of the lower pole with the presence of an area with a worse accumulation of the radiotracer) (Figure 1).

Two months later moderately elevated blood pressure (BP) in-home measurements were observed and at the age of 17.75 years, the patient was referred to the Department of Paediatric Nephrology with suspicion of arterial hypertension. Physical examination revealed central obesity (body weight 103.6 kg > 97th percentile, height 167 cm 50th-75th percentile, BMI 37.15 kg/m² > 97th percentile), lipomastia, poorly developed mammary glands, hirsutism, dark keratosis in the neck and armpits, facial dysmorphism (receding chin, almond-shaped eye gaps, slight hypotelorism, short, slightly rotated auricles, high-arched palate), short neck, divergent strabismus of the right eye (Figure 2), scars of the 5th toes after removal of additional toes, vestigial fingers in the form of skin processes on the 5th fingers, and bilateral cutaneous syndactyly of 2nd and 3rd toes (Figure 3).

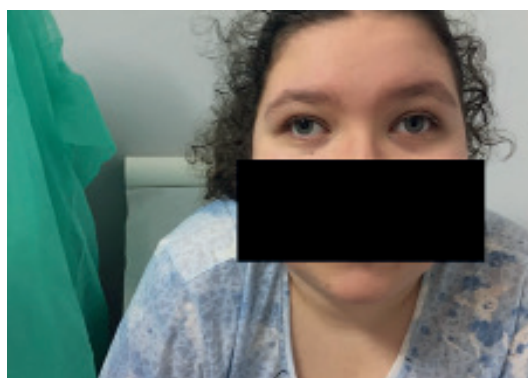


FIGURE 2. The face of the presented patient. Note the dysmorphic features, divergent strabismus of the right eye, and short neck



FIGURE 3. Left hand and feet of the presented patient. Note the vestigial finger in the form of skin process on the 5th finger (arrow) and bilateral cutaneous syndactyly of the 2nd and 3rd toes (arrows), more severe in the right foot

Automatic 24-hour blood pressure monitoring confirmed the diagnosis of stage 1 hypertension. Average values of BP were 137/81 mmHg, 144/87 mmHg, and 120/66 mmHg with systolic BP load: 81%, 84%, 73%, diastolic BP load: 62%, 61%, and 64% in 24 hours, daytime and night-time periods, respectively. Effective treatment with amlodipine at a daily dose of 10 mg was initiated. Laboratory tests showed hyperuricaemia (7.98 mg/dl), hypercholesterolaemia (216 mg/dl) and hypertriglyceridaemia (258 mg/dl), and borderline fasting plasma glucose (99 mg/dl). Kidney function (creatinine 0.75 mg/dl, eGFR 122.5 ml/min/1.73 m² – estimated with Schwartz formula), urinalysis, and blood levels of renin, aldosterone, cortisol, adrenocorticotrophic, thyroid, and sex hormones were normal. An ophthalmological evaluation revealed amblyopia and night blindness especially in the right eye, local hyperpigmentation, and single point depigmentation on the peripheral parts of the retina. Due to the suspicion of papilledema, an MRI of the head and optic nerves was performed, which revealed empty sella syndrome (Figure 4).

On the basis of the overall clinical picture, BBS was suspected and confirmed by whole exome (WES) and Sanger sequencing (homozygous mutation of the *BBS5* gene NM_152384.2:c.[619-1G>C];[619-1G>C]).

DISCUSSION

Bardet-Biedl syndrome is a heterogeneous autosomal recessive condition named after the French physician Georges Louis Bardet and the Hungarian endocrinologist and pathologist Artur Biedl. To date, 26 BBS-causing genes have been identified, and their mutations comprise 80% of cases with a clinical diagnosis of BBS [2, 3]. BBS is rare, with an incidence of around 1 : 100,000 in Europe and North America [4]. So far, the mechanism of the genetic and clinical diversity in Bardet-Biedl patients is not fully understood. BBS is secondary to central cilia structure defects. Cilia are the omnipresent organelles functioning primarily for cell-to-cell signalling, and their integrity is crucial for various developmental signalling pathways, which explains the multi-system involvement in BBS.

The description of cardinal clinical manifestations and subsequent diagnostic criteria of BBS were mainly created based on an influential study by Beales *et al.* [1]. The diagnostic algorithm was conceived before the detection of genes associated with this syndrome. The diagnosis relies on the number of primary and secondary phenotypic features of BBS [5-7]. They are listed in Table 1 with information about their occurrence in the presented patient.

It is proposed that BBS is diagnosed in patients with at least 4 out of 6 primary BBS features. If only 3 primary features are detected, 2 secondary features are necessary to confirm the disease [5]. Our patient had 5 primary BBS features apart from hypogonadism, which is more common in boys. In our case, the structure of the genitals was



FIGURE 4. Magnetic resonance imaging of the head of the presented patient. Note the herniation of the suprasellar reservoir into the sella turcica with flattening of the pituitary gland – CC size approx. 2 mm – empty sella syndrome – arrow (Department of Paediatric Radiology, Medical University of Lublin)

normal, although delayed puberty and poorly developed mammary glands were present. The numerous accompanying secondary features of BBS in our patient are listed in Table 1. It is well documented that symptoms may significantly vary between affected individuals. However, almost all clinical studies analysed patients of different ages. In many individuals with BBS at birth, only polydactyly is observed. Other symptoms of BBS tend to occur gradually during the following years of life; thus, patients diagnosed in early childhood tend to have fewer clinical features of the disease [1, 8]. In our case, polydactyly and syndactyly were noticeable at birth. At that time an ultrasound examination was not performed, so renal anomalies were not found. The prevalence of kidney disease in BBS patients is 53-82%. Our patient has right kidney ectopy and hypoplasia with normal e-GFR. Although classically BBS is associated with polycystic kidney disease, a typical renal manifestation of ciliopathies, only 30% of patients with renal involvement have cystic or dysplastic changes. The remainder have hydronephrosis or, like in our case, developmental abnormalities including unilateral agenesis, renal ectopy, horseshoe kidney, foetal lobulation, calyceal clubbing, or vesicoureteral reflux. About 8% of them develop end-stage renal disease [1, 9].

Other symptoms, such as obesity, vision deterioration, strabismus, facial dysmorphism, and learning difficulties, occurred in the first decade of life. Additionally at the age of 10 years renal ectopy was diagnosed. Although the girl met the diagnostic criteria of BBS, despite multidisciplinary care, BBS was not suspected at the time. Only delayed puberty and the features of the metabolic syndrome resulted in detailed endocrinological diagnostics and genetic consultation. After excluding Prader-Willy syndrome, testing for other genetic syndromes associated with obesity including BBS was suggested. Eventually, 3 months before adulthood, elevated blood pressure occurred and the patient was

TABLE 1. Diagnostic features of BBS and their occurrence and age of diagnosis in the presented patient

Primary feature	Our patient		Secondary feature	Our patient	
	Presence	Age (years)		Presence	Age (years)
Rod-cone dystrophy (<i>retinitis pigmentosa</i>)	Local hyperpigmentation and single point depigmentation on the peripheral parts of the retina	17.75	Brachydactyly or syndactyly	+	At birth
	Night blindness		Dental defects	–	
			Developmental delay	+	7
			Speech deficit	+	7
			Ataxia/poor coordination	–	
			Olfactory deficit	–	
			Diabetes mellitus	Glucose intolerance, hyperinsulinemia	17
Polydactyly	+	At birth			
Obesity	+	2-3			
Renal defects	+	10	Strabismus/cataracts/astigmatism	+/-/+	5
Hypogenitalism	Delayed puberty	17	Hypertension	+	17.75
Learning difficulties	+	7	Liver abnormalities	–	
			Bronchial asthma	–	
			Craniofacial dysmorphism	+	17

referred to our clinic, where based on the overall clinical picture, BBS was suspected. It was confirmed by genetic testing, which revealed mutations in the BBS5 gene, which account for 3.7% of all BBS cases [3]. The homozygous c.619-1G>C variant detected in our patient was previously reported in the ClinVar database.

Ophthalmological consultation, beyond earlier diagnosed poor vision, night blindness, and strabismus, revealed abnormalities of retinal pigmentation, and due to the suspicion of papilloedema, an MRI of the head was performed, which showed empty sella syndrome. The presence of this condition was previously described in patients with Bardet-Biedl syndrome by Soliman *et al.* [10].

Most patients with BBS are diagnosed in late childhood or early adulthood, although later diagnosis is not uncommon and is reported in the literature. Santos *et al.* described 4 adult patients with BBS diagnosed in a dialysis centre [11]. In some cases, highly variable expression, even among siblings, makes the diagnosis difficult and often delayed [12]. Despite the typical clinical presentation of BBS, the correct diagnosis was made in our patient with a long delay, at the age of 17.75 years.

The management of BBS is presently symptomatic, concentrating on appropriate treatment of metabolic syndrome, diabetes, and hypertension to minimize late complications [13]. Although for BBS patients dietetic input provides the safest and most effective weight-loss strategy, in some cases bariatric surgery may be necessary [14]. In our patient hypotensive treatment was successful although

poor weight control and non-compliance with dietary recommendations hindered the treatment.

Despite the incurable nature of the disease, its early diagnosis and appropriate management may improve the prognosis. Moreover, it enables targeted counselling with other family members, especially carriers of heterozygous mutations of BBS genes, who are at increased risk of urinary tract malformations and kidney cancer [15].

CONCLUSIONS

The presented case is an example of a late diagnosis of BBS. Only a comprehensive analysis of clinical symptoms in affected patients allows a correct diagnosis.

DISCLOSURE

The authors declare no conflict of interest.

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